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	E: Sleep, Circadian and Neuroendocrine Mechanisms
	F: Nervous System Disorders
	G: Methods and Techniques
	H: Autonomic Nervous System

Poster Session 1
Sunday 12 April 2015
Posters P1-A-001 to P1-H-006

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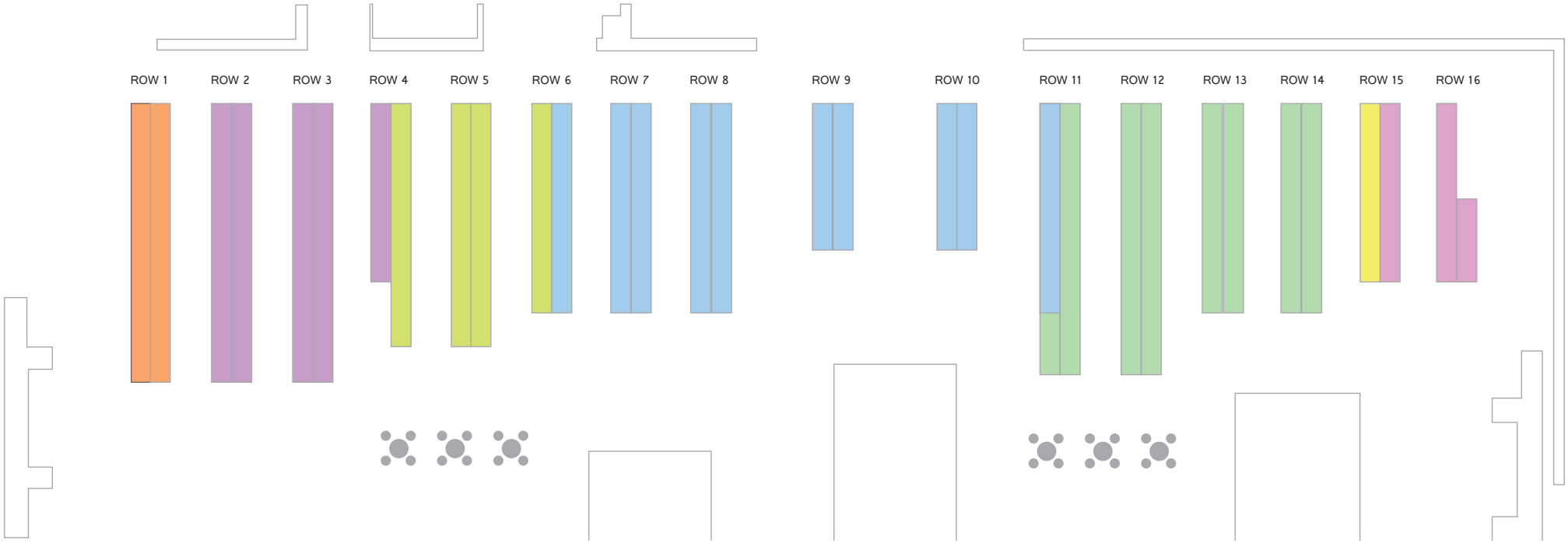
NEUROSCIENCE

BNA 2015 POSTER DISPLAY DAY 1
SUNDAY 12 APRIL



- A: Development
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Theme A: Development

Posters P1-A-001 to P1-A-020

Poster Ref: P1-A-001

Theme: A: Development

Can oxytocin be of any therapeutic use in the future? – A meta-analysis on the potential therapeutic role of oxytocin in children and youths with autism spectrum disorder (ASD).

Baguiasri Mandane

De Montfort University

Objectives: Oxytocin is a nonapeptide hormone synthesised mostly by the neurons in the paraventricular and supraoptic nucleus of the hypothalamus; it is then released into the bloodstream by the posterior pituitary. The neuropeptide hormone, which is mainly involved in promoting maternal behaviour, has further also been widely studied as a potential for treatment of social deficit symptoms in many neurological disorders such as autism and personality disorders. This meta-analysis was carried out to examine whether the following hypothesis was true: “oxytocin enhances emotion recognition in children and youths with ASD”. The aim was to see the impact of oxytocin administration (short-term) on social deficit symptoms in children suffering from ASD on a wider scale.

Review Method: The key words researched included: ASD; Autism; Oxytocin; Intranasal oxytocin; Children; Youths; RMET; Social; Short-term. The collected data was then analysed using Review Manager 5.2 program.

Results: The results from this meta-analysis did not show a statistically significant benefit for the use of oxytocin in young people diagnosed with ASD compared to placebo at the 95% confidence interval ($P=0.92 > 0.05$). Potential reasons for these negative findings could take account of contextual and interindividual differences which might have affected the principal effects of oxytocin and its levels in the periphery. Contextual differences include for example the presence of a stranger versus a friend and interindividual factors such as gender, attachment style or the presence of existing psychiatric symptoms. Additionally, single nucleotide polymorphisms leading to a genomic deletion or unusual methylation of the oxytocin receptor gene could have also been implicated in the lack of response.

Conclusion: This meta-analysis did not statistically verify the hypothesis that oxytocin enhances emotion recognition in children and youths suffering from ASD. However, this interpretation needs to be evaluated with caution, as the trials used in this meta-analysis were fairly small. Future studies comparing gender, genetics, hormonal status and also individual differences are certainly needed to further enhance our knowledge and understanding of the aetiology of autistic spectrum disorders.

Poster Ref: P1-A-003

Theme: A: Development

An *in vitro* model of the impact of chemotherapy on neural stem cells and the protection provided by cells in the neurogenic niche.

Entedhar Kadhum Huss Rabiaa, Ayesha Maqbool, Ayoub Al-Bayati, Paul Smith and Peter Wigmore

University of Nottingham

Numerous patient reports have complained about cognitive decline after chemotherapy treatment. These effects have been called “chemobrain” or “chemofog” and while not affecting all patients can persist for many years after the completion of treatment. Animal studies have found that the systemic chemotherapy causes a persistent reduction in adult hippocampal neurogenesis. As hippocampal neurogenesis is required for the consolidation of long term memory this is likely to be one of the causes of cognitive decline. Hippocampal neurogenesis requires the proliferation of neural stem cells in the subgranular zone of the dentate gyrus. Many of these stem cells are in close contact with blood vessels and astrocytes which form components of the neurogenic niche which regulates neurogenesis. After chemotherapy, proliferating cells in contact with blood vessels, survive better than cells some distance from blood vessels suggesting that association with this tissue provides protection from chemotherapy. We have developed an in-vitro model to study the protective effect of different combinations of neural and non neural cells. Neural stem cells are more sensitive to chemotherapy (5-Fluorouracil) in comparison to endothelial or glial cells. Co-culture of neural cells with endothelial and glial cells protects neural stem cells from chemotherapy in contrast to co-culture with non neural cells (3T3). Both endothelial and glial cells require cell to cell contact with neural stem cells to provide protection with glial cells providing the most protection. We are currently studying the mechanisms by which endothelial and glial cells regulate neural stem cell proliferation *via* cell to cell contact.

Poster Ref: P1-A-004

Theme: A: Development

The role of transcription factor Pax6 in the development of the ventral lateral geniculate nucleus.

Ziwen Li, Tian Tian, Martine Manuel, Tom Pratt and David Price

University of Edinburgh

The development of diencephalon can be summarized as a process in which cells that initially appear similar give rise to a complex structure that contains a variety of cell groups called nuclei. The nuclei execute distinct functions. The ventral lateral geniculate nucleus (vLGN) is involved in the visual system.

The transcription factor Pax6 is involved in the development of structures including cortex, diencephalon and major axonal tracts in the forebrain. Pax6-/- mouse mutants, also known as Small eye (Sey) mutants, show severe defects in the embryonic forebrain. The disrupted structure of the diencephalon hinders us from further investigating its detailed structures.

In this study, we use the Cre-loxP system to mutate Pax6 conditionally using Zic4Cre, with a GFP reporter to show the Cre activity. Zic4 is a transcription factor mainly expressed in septum, hem, thalamus and prethalamus. The deletion of Pax6 is restricted to lineages that express Zic4. A relatively normal forebrain is maintained. With the help of this model, we investigated the development of specific thalamic nuclei, including the vLGN.

Staining of GFP on postnatal day (P) 0 coronal brain sections showed a distinct distribution of Zic4 lineage cells: they aggregate in greater density into the vLGN than into the adjacent nuclei such as dorsal lateral geniculate nuclei (dLGN) and ventral posterior nuclei (VP). We found Pax6 deletion causes Zic4 lineage cell density to decrease in the vLGN of the Pax6fl/fl mutants but to increase in that of the Pax6fl/+mutants. An increase of Zic4 lineage cell density was also observed in dLGN of both the Pax6fl/fl and Pax6fl/+ mutants. VP is not significantly affected by the Pax6 deletion. These findings indicated that the transcription factor Pax6 is involved in the development of the lateral geniculate complex and may play a role in cell parcellation in the diencephalon by regulating cell distribution.

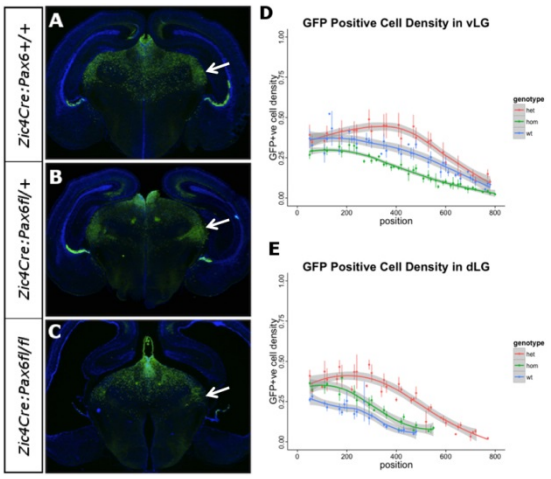


Figure GFP staining on P0 coronal sections from Zic4Cre:Pax6+/+ (wt), Zic4Cre:Pax6fl/+ (het) and Zic4Cre:Pax6fl/fl (hom) mouse brains. There are more GFP+ve cells in the vLGN in het (arrow, B) than in that of wt (arrow, A) and the fewest in hom vLGN (arrow, C). Comparisons of GFP+ve cell density (cells/100 miron2) in vLGN (D) and dLGN (E) between genotypes at a range of rostrocaudal positions.

Poster Ref: P1-A-005

Theme: A: Development

Influence of white matter connections on cortical gyrification.

Yujiang Wang, Peter Taylor and Marcus Kaiser

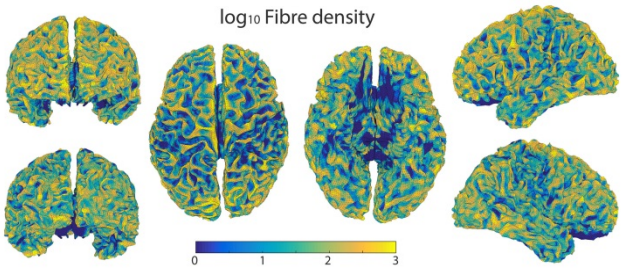
Newcastle University

Purpose: The mechanisms underlying cortical gyrification have been subject of debate for nearly two decades. One school of thought theorises that the mechanical forces exerted by white matter fibres as the major driver of gyrification. Here we specifically test the predictions inferred from three major white matter theories.

Methods: Using high-resolution diffusion spectrum imaging data to infer the white matter fibres, and combining it with information on the geometry of the cortex, we investigate if any support can be found for the white matter theories.

Results: We systematically tested the predictions made by the major white matter theories regarding the fibre density and the curvature of the white matter surface. None of the predictions could be validated. Rather, our data indicates that the geometry of the cortex is the result of many interacting factors (e.g. cortical thickness, cortical region, axonal density). Among these processes, the mechanical forces exerted by white matter fibre tracts are not the major driver of cortical gyrification.

Significance: We suggest an indirect effect of white matter tracts on cortical folding. We discuss that the possible developmental processes shaping cortical geometry could be genetically determined cortical expansion, white matter input dependent cortical expansion, and function dependent cortical expansion.



Fibre density distribution on the white matter surface.

Poster Ref: P1-A-006

Theme: A: Development

Determining whether myelin sheath length is an inherent property of oligodendrocytes.

Lauren Byrne, Marie Bechler and Charles ffrench-Constant

MRC Centre for Regenerative Medicine, University of Edinburgh

The functions of the vertebrate central nervous system (CNS) rely upon the ability to rapidly conduct neuronal impulses, which is achieved by wrapping axons with insulating layers of myelin sheath. Conduction velocity along an axon is affected by the length of myelin sheaths, so regulating this length provides a way of co-ordinating the timing of signals between different CNS regions. However, what determines sheath length is largely unknown. Myelin sheath length varies in different CNS regions; this may be due to environmental differences in these regions or alternatively, as hypothesised in this study, it may be that sheath length is inherent to oligodendrocytes and distinct populations produce sheaths of different lengths. To test this, a neuron-free 3-D culture system has been utilised in which synthetic microfibres provide a substrate for myelination. This allows us to determine the intrinsic properties of oligodendrocytes in the absence of axonal cues. Oligodendrocyte progenitor cells (OPCs) isolated and enriched from the neonatal rat cortex and spinal cord, were cultured on multiple microfibre diameters and sheath length was measured. The average sheath length produced by spinal cord OPCs was almost twice that of cortical OPCs and lengths were comparable to those seen in-vivo in these regions. Oligodendrocytes were also found to have an inherent ability to respond to differences in microfibre diameter, producing longer sheaths on larger diameter microfibres. The results support our hypothesis that myelin sheath length is intrinsically regulated by oligodendrocytes and that functionally-distinct oligodendrocyte populations exist in the cortex and spinal cord.

Poster Ref: P1-A-007

Theme: A: Development

Longitudinal changes in hippocampal volume in the Edinburgh high risk study of schizophrenia.

Catherine Bois[1], Levita Liat[2], Ripp Isabelle[3], Whalley Heather[1] and Stephen Lawrie[1]

[1]University of Edinburgh, [2]University of Sheffield, [3]University of Cologne, Germany

Introduction: Schizophrenia is associated with structural brain abnormalities that are likely to be present before disease onset. It remains unclear to what extent these represent general vulnerability indicators or are associated with the developing clinical state itself. It also remains unclear whether such state or trait alterations may be evident at any given time-point, or whether they progress over time.

Methods: To investigate this, structural brain scans were acquired at two time-points (mean scan-interval 1.87 years) in a cohort of young unaffected individuals at high familial risk of schizophrenia (baseline, n =142; follow-up, n = 64) and healthy controls (baseline, n = 36; follow-up, n = 18). Sub-cortical reconstructions of the hippocampus and amygdala were generated using the longitudinal pipeline available with Freesurfer. The high risk cohort was subdivided into individuals that remained well during the study, (HR[well], baseline, n = 68; follow-up n = 30), transient and/or partial symptoms that were insufficient to support a formal diagnosis, (HR[symp], baseline, n = 57; follow-up, n = 26)) and individuals that subsequently developed schizophrenia according to ICD-10 criteria, (HR[ill], baseline n = 17; follow-up, n = 8). Longitudinal change in the hippocampus was compared, focusing first on overall differences between high-risk individuals and controls and then on sub-group differences within the high-risk cohort.

Results: We found a significantly altered developmental trajectory for all high risk individuals compared to controls, with controls showing a significant increase in hippocampal volume over time compared to those at high risk ($F = 13.82$, $df = 1,320$, $p = .0002$). We did not find evidence of altered longitudinal trajectories based on clinical outcome within the high risk cohort.

Discussion: Our results suggest that an altered developmental trajectory of hippocampal volume is associated with a general familial predisposition to develop schizophrenia, as this alteration was not related to subsequent clinical outcome, and may thus reflect a trait marker of schizophrenia.

Poster Ref: P1-A-008

Theme: A: Development

A longitudinal study of global cortical morphology in the Edinburgh high risk study of schizophrenia.

Catherine Bois[1], Lisa Ronan[2], Liat Levita[3], Heather Whalley[1], Andrew MacIntosh[1] and Stephen Lawrie[1]

[1]University of Edinburgh, [2]University of Cambridge, [3]University of Sheffield

Background: Schizophrenia is associated with global structural brain abnormalities, but most studies have analysed cortical gray matter volume, rather than its constituents of surface area and cortical thickness, potentially obfuscating their distinct contributions in the pathophysiology of schizophrenia. In the present study we therefore explored their relationships in 146 individuals at high genetic risk of schizophrenia as some became ill, and 36 control subjects.

Methods: Participants received detailed clinical assessment and structural images for all subjects were acquired at two time-points and processed using Freesurfer v 5.0 (mean scan-interval = 1.87 years). Any longitudinal change in left and right cortical thickness and surface area was then investigated using mixed effects analysis of variance.

Results: At baseline , there were no significant differences in thickness between groups. However there were significant differences in surface area, attributed to larger surface areas in HR[symp] and HR[ill] compared to HR[well], ($F = 2.80$, $df = 165$ $p < .05$). Longitudinally, cortical shrinkage occurred in HR[ill] only, whilst HCs underwent larger decreases in surface area compared to all HR groups ($F = 4.35$, $df = 338$ $p < .001$).

Discussion: Baseline surface area measures distinguish HR[symp] and HR[ill] from HR[well], whilst the trajectory of SA reduction is different in HC compared to all HR individuals. However, global cortical thinning occurred only in HR[ill], suggesting that dynamic brain changes occur bilaterally across the whole cortex before the onset of psychosis.

Poster Ref: P1-A-009

Theme: A: Development

Investigating the expression of voltage-gated calcium channels during axon myelination.

Entisar Elsaeedi[1], Robert Fern[2] and Claire Gibson[1]

[1]University of Leicester, [2]University of Plymouth

Voltage-gated calcium channels (VGCCs) have been shown to be expressed in central axons as they begin myelination. During the onset of central myelination VGCCs are reported to contribute to action potential conduction. However, it is unknown whether this is unique to central axons or the same pattern occurs in peripheral axons or unmyelinated axons at the optic nerve head. Immunohistochemistry was used to investigate the expression of VGCCs in the peripheral nervous system using P0, P10, P20 and adult rat sciatic nerve preparations. Antibodies were used for: α_1a, α_1c, α_1d and $\alpha_2\delta_2$ subunits in addition to antipan-Ca^{++} channel and monoclonal antipan-Na^{+} channel. Neurofilaments were also co-stained with VGCCs using anti-neurofilament light (70 Dk). The data show that L-type and P/Q-type channel subunits were present at low levels at P0 and increased by P10 after which there was a decline in their expression and they were almost absent by P20. Na+ channel clusters were only evident at P10 and continued to increase in expression by P20. In addition, the presence of clusters of both L-type and P/Q-type channels were demonstrated in unmyelinated axons at the head of the optic nerve and in the retina. Thus, these results demonstrate that, during development, VGCC's are expressed on peripheral axons as well as central unmyelinated axons. The expression of P/Q-type calcium channels increased around the onset of myelination and node of Ranvier formation. Thus, these calcium channels may play an important role in the signalling pathways that are involved in the development and modulation of peripheral axons.

Poster Ref: P1-A-010
Theme: A: Development

Role of differential heparan sulfate sulfation in mouse forebrain development.

Wai Kit Chan, James Clegg, David Price and Thomas Pratt
Centre for Integrative Physiology, University of Edinburgh

Heparan sulfate proteoglycans (HSPGs) are cell surface/secreted molecules expressed by all cells. HSPGs consist of linear heparan sulphate (HS) carbohydrate side-chains attached to a core protein and are involved in regulating key signalling pathways in the developing mammalian brain *via* sugar-protein interactions. HS has an enormous variety of structures due to postsynthetic modification. It has been hypothesised that specific interactions between HSPGs and signalling molecules are encoded by differential enzymatic sulfation of the HS side-chain. Hs2st and Hs6st1 are two heparansulfotransferase enzymes involved in generating different HS structures by sulfating the 2-carbon or 6-carbon molecule of the uronate or glucosamine moieties of the HS sugar backbone respectively. Loss of either Hs2st or Hs6st1 function has profound, but distinct, consequences for forebrain development confirming the importance of each type of HS sulfation.

Fibroblast growth factor (Fgf) is a family of signalling molecules crucial for forebrain development. Some of its members such as Fgf8 are morphogens which patterns the forebrain *via* regulated gradient formation while others for example Fgf2 drives neurogenesis and cell proliferation. HS has been previously shown to be involved with these processes however, the role differential sulfation plays in these processes and the molecular mechanism(s) behind this has not been clearly resolved. We used a combined *in vivo* and *in vitro* approach to investigate the role of differential sulfation in mice with Hs2st or Hs6st1 loss of function. Here we report how differential HS sulfation regulates properties of Fgf signalling during forebrain development. These data provides us with further insight into the role of HS in the complex but precise regulation of mouse forebrain development.

Poster Ref: P1-A-011

Theme: A: Development

What is the role of the retrosplenial cortex in solving spatial alternation problems?

Anna Powell, Andrew Nelson, Seralynne Vann and John Aggleton

School of Psychology, Cardiff University

The retrosplenial cortex (RSC) shares dense reciprocal connections with the hippocampus and anterior thalamic nuclei, regions required for spatial alternation. Furthermore, there is a large body of evidence supporting a role for the RSC in spatial learning and navigation. It is surprising, therefore, that lesions in this region have little effect on T-maze alternation performance. Here, we tested the hypothesis that compensatory mechanisms, for example a switch in cue strategy (e.g. from extra- to intra-maze cues), may mask any alternation deficits in RSC-lesioned animals. Consistent with this hypothesis, we show that post-training, temporary inactivation of the RSC by muscimol produced a striking deficit on standard T-maze alternation. Importantly, by using fluorescent-conjugated muscimol, we confirm that the infusion site was restricted to the RSC, with no evidence of diffusion into the dorsal hippocampus or dorsal subiculum. One interpretation of these results is that the role of the RSC in spatial alternation may be masked by compensatory mechanisms, for example by utilising a different set of navigational cues, which develop over the course of training. Conversely, after learning to rely on a specific set of cues, alternation behaviour becomes acutely sensitive to RSC damage, suggesting an inability to switch between different cue types.

Poster Ref: P1-A-012

Theme: A: Development

The role of Hippo/YAP signalling in Schwann cell development and myelination.

Katherine North, Thomas Mindos, Xing-Pen Dun and David Parkinson

Plymouth University Peninsula School of Medicine and Dentistry

Schwann cells are the main glial cells of the peripheral nervous system (PNS) and myelinate neurons in a one-to-one relationship. The signals that control Schwann cell proliferation during both development and after injury are not yet understood, which led us to investigate the role of the Hippo signalling pathway. The conserved Hippo signalling pathway has been shown to regulate organ size in both *Drosophila* and mammals. In mammalian cells, YAP and its transcriptional co-activator TAZ are found downstream of the Hippo pathway kinase cascade, activation of which causes their inhibition *via* phosphorylation and cytoplasmic retention. Using a Schwann cell-specific knockout of the YAP effector of the Hippo pathway we have studied the role of this protein in Schwann cell proliferation and differentiation *in vivo*. Loss of the tumour suppressor Merlin causes, in many cell types, activation of the Hippo signalling pathway and nuclear localisation of the YAP protein. Loss of Merlin in Schwann cells causes a large increase in Schwann cell proliferation and defects in axonal regeneration after injury. We are currently investigating the role of the YAP protein in these effects.

Poster Ref: P1-A-013
Theme: A: Development

Analysis of hypothalamic developmental changes in Gnasxl knock-out mice.

Thomas Leather[1], Andrew Holmes[2], Patricia Thomas[2], Kimi Omolokun[2], Kirsty Johnson[2], Seham Alsaif[2], Niamh Horton[2], Joao Pedro De Magalhaes[3] and Antonious Plagge[2]
[1]University of Liverpool, [2]Institute of Translational Medicine, University of Liverpool, UK, [3]Institute of Integrative Biology, University of Liverpool

Gnasxl is an alternative transcript of the Gnas locus and encodes an NH2-terminally extended form (XLαs) of the stimulatory G-protein α-subunit Gαs. XLαs activates the adenylyl cyclase/cAMP signalling pathway. An imprinted gene on mouse chromosome 2 and conserved in human, it is expressed monoallelically, from the paternal allele, in a subset of hypothalamic nuclei that are involved in the regulation of energy homeostasis and sympathetic nervous system (SNS) activity (Arcuate, Dorsomedial, Paraventricular and Lateral nuclei). Gnasxl knock-out (KO) mice display a high postnatal mortality rate, poor suckling and growth retardation. As adults they show a lean and hypermetabolic phenotype, indicating that XLαs is required for normal postnatal development and adult regulation of energy metabolism. Gnasxl KOs also display increased SNS activity, causing elevated body temperature, glucose and lipid metabolism.

To investigate changes in gene expression, we undertook RNAseq analysis (Illumina) of total RNA from adult hypothalami. Data were verified by qRT-PCR and immunohistochemistry (IHC).

We identified Glial Fibrillary Acidic Protein (Gfap) as a 2-fold downregulated transcript in Gnasxl KO hypothalami (RNAseq $p<0.0001$; qRT-PCR $p<0.05$). Additionally, we found a 2-fold increase in expression of the signalling form of the Leptin receptor (Lepr-b) (qRT-PCR $p<0.05$). IHC of adult hypothalamus sections revealed a reduction in Gfap-positive cell numbers of 16% (anterior and central) to 41% (posterior regions) ($p<0.01$). This included Gfap-positive astrocytes and subpopulations of ependymal tanycytes. Since Gnasxl is not expressed in glial cells, we investigated whether the changes develop as a consequence of the early postnatal failure-to-thrive phenotype of the KOs. At age P15 we did not find a significant difference in Gfap-positive cells. Glial cells and tanycytes participate in the blood-brain-barrier (BBB). We are currently investigating BBB function through uptake and diffusion of Evans Blue from the circulation into the ventrobasal hypothalamus.

Our findings of reduced Gfap expression and glial cell numbers hint at an abnormal postnatal hypothalamic development in lean Gnasxl KO mice. The data complement findings of gliosis and elevated Gfap levels in obese mice.

Poster Ref: P1-A-014

Theme: A: Development

The role of heparan sulphotransferase enzymes Hs2st and Hs6st1 in corpus callosum development.

James Clegg and Thomas Pratt

University of Edinburgh

Heparan sulphate proteoglycans (HSPGs) are complex macromolecules that are found at the cell surface and form part of the extracellular matrix. HSPGs play a crucial role in the modulation of a number of different cell-cell signalling pathways during development; these include the signalling of axon guidance molecules such as Slit/Robo. HSPGs consist of a core protein to which heparan sulphate side chains are added, these side chains are modified by the addition and removal of sulphate groups at specific positions on the carbohydrate ring. It has been proposed that differential sulphation of these HS side chains by sulphotransferase enzymes may change the ability of cells or axons to respond to particular signalling molecules. This may help explain how a relatively small number of axon guidance molecules are able to guide the enormous number of axons within the brain. The corpus callosum (CC) is a large axon tract which links the cerebral hemispheres. Previously we have shown that in mice which lack the HS modifying enzymes Hs2st and Hs6st1 the CC fails to form. It remains unclear however whether this defect is primarily caused by a loss of HS sulphation at the growth cone of the callosal axons or whether the change in sulphation affects the midline environment through which these axons navigate. To answer this question we have used conditional mutagenesis and organotypic culture techniques to specifically ablate the expression of Hs2st or Hs6st1 in callosal projection neurons or populations of cells at the telencephalic midline and examined the effect this has on development of the CC.

Poster Ref: P1-A-015

Theme: A: Development

Structural asymmetries, handedness and neurodevelopmental disorders: a complex link revealed by genetics.

Silvia Paracchini[1], William Brandler[2], Andrews Morris[2], David Evans[3], Susan Ring[3], John Stein[2], Joel Talcott[4], Simon Fisher[5] and Caleb Webber[2]

[1]University of St Andrews, [2]University of Oxford, [3]University of Bristol, [4]Aston University, [5]Max Planck Institute for Psycholinguistics

Most people can easily say which hand they prefer for writing but very little is known of what determines handedness and many of the features associated to this lateralised behaviour. Worldwide, the frequency of left-handers is approximately 10%, and it is not clear what is at the basis of this remarkable population bias. Handedness is a heritable trait, but, despite well-powered studies, no genes have been convincingly implicated in hand preference. Handedness has been suggested to reflect cerebral asymmetries and to be linked to the human ability to speak, observing that language is also strongly lateralised.

We recently reported a genome-wide association study (GWAS) for a quantitative measure of handedness and dexterity (pegboard) in individuals with dyslexia (n = 728). The strongest association ($P < 0.5\times10\text{-}8$) is located within the PCSK6 gene, known to activate NODAL, which is required to regulate left/right body axis determination. GWAS pathway analysis, based on gene-set enrichment strategies, showed that left/right asymmetry pathways are associated with handedness in both the dyslexia and a general population (n = 2666) cohorts. In particular, genes involved in corpus callosum development were enriched among the GWAS top hits (Brandler et al 2013). Furthermore, different markers at the PCSK6 locus were found to be associated with a measure of handedness in a completely independent study (Arning et al 2013).Our dat acontribute to exclude a single gene model controlling handedness.

We propose that handedness is a polygenic trait controlled, at least partly, by the molecular mechanisms which establish structural asymmetry early in development, which might be implicated in neurodevelopmental disorders.

We are now investigating the molecular mechanisms underlying this association using neuronal stem cell and zebrafish models. Preliminary data shows genetic variation at the PCSK6 locus might control a novel noncoding RNA. Furthermore we are collecting the pegboard measure in large cohorts deeply characterized at phenotypic level and with different ethnical origin, to evaluate the cross-linguistic effects of the PCSK6 association and to map additional loci implicated in handedness.

Poster Ref: P1-A-016

Theme: A: Development

Canalisation of neuronal network activity patterns confers robustness against synaptic perturbations.

Andrew Morton[1], Paul Charlesworth[2], Stephen J. Eglen[3], Noboru H. Komiyama[4] and Seth G. N. Grant[4]

[1]University of Edinburgh, [2]Department of Physiology, Development and Neuroscience, University of Cambridge, [3]Department of Applied Mathematics and Theoretical Physics, University of Cambridge, [4]Centre for Clinical Brain Sciences, University of Edinburgh

Genome sequencing studies suggest that normal individuals carry hundreds of potentially damaging mutations. Brain development and the establishment of optimal intrinsic firing patterns therefore show significant resilience to mutation, as well as environmental perturbations. Technical constraints have so far limited the ability to study the effects of mutations on the development of firing patterns. To this end, we developed a high-throughput electrophysiology platform for analysing neuronal network activity in a pipeline of transgenic mice carrying targeted deletions of synaptic genes. From hippocampal neurons cultured on multi-electrode arrays, we made longitudinal recordings of spontaneous network activity over a four-week period of development *in vitro*. Developmental profiles of six quantitative parameters that describe overall levels and patterns within network activity were analysed. Wild-type cultures exhibited increasing spontaneous network activity levels that plateaued after approximately 21 days *in vitro* (DIV). Over the same time period, spikes became increasingly entrained within bursts, which showed increasing network-wide synchronisation and periodicity at theta frequency. We initially studied the effects of deletion of the principal AMPA-receptor subunit, Gria1 and chronic pharmacological blockade of NMDA receptors with APV. Network activity patterns were severely disrupted by both these perturbations during the first 14 DIV. Unexpectedly however, with continuing development, activity patterns converged on those routinely observed in wild-type cultures. Smaller effects on early firing patterns were observed in cultures from mice carrying knockout mutations in other synaptic genes. The unifying feature of the data overall was that disruptions in intrinsic firing patterns observed early in development were buffered, such that they converged on wild-type patterns by maturity. We propose therefore that the development of optimal intrinsic firing patterns is a highly canalised property of neuronal networks. This may be illustrative of the robustness of brain development to mutation and environmental perturbation.

Poster Ref: P1-A-017

Theme: A: Development

Developmental time windows for axon growth influence neuronal network topology.

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Early brain connectivity development consists of multiple stages: birth of neurons, their migration and the subsequent growth of axons and dendrites. Each stage occurs within a certain period of time depending on types of neurons and cortical layers. Forming synapses between neurons either by growing axons starting at similar times for all neurons (much-overlapped time windows) or at different time points (less-overlapped) may affect the topological and spatial properties of neuronal networks. Here, we explore the extreme cases of axon formation especially concerning short-distance connectivity during early development, either starting at the same time for all neurons (parallel, i.e. maximally-overlapped time windows) or occurring for each neuron separately one neuron after another (serial, i.e. no overlaps in time windows). For both cases, the number of potential and established synapses remained comparable. Topological and spatial properties, however, differed: neurons that started axon growth early on in serial growth achieved higher out-degrees, higher local efficiency, and longer axon lengths while neurons demonstrated more homogeneous connectivity patterns for parallel growth. Second, connection probability decreased more rapidly with distance between neurons for parallel growth than for serial growth. Third, bidirectional connections were more numerous for parallel growth. Finally, we tested our predictions with *Caenorhabditis elegans* data. Together, this indicates that time windows for axon growth influence the topological and spatial properties of neuronal networks opening the possibility to a posteriori estimate developmental mechanisms based on network properties of a developed network.

Poster Ref: P1-A-018

Theme: A: Development

Genes involved in secondary motor neuron development and axon differentiation in zebrafish.

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Motor axons grow out of the spinal cord in a motor neuron subtype specific manner and innervate different muscle groups to facilitate locomotor movements. To find genes and important pathways involved in motor neuron generation and axon development in zebrafish, we conducted an ENU-induced mutagenesis screen in islet-1:GFP transgenic zebrafish, in which a subset of dorsally projecting motor neurons is labelled. We have discovered 6 mutants displaying delayed or inhibited appearance of secondary motor neurons and/or motor axon deficits among 111 F2 families screened. We are currently determining the specificity of islet-1:GFP motor/axon phenotypes and are characterising the affected signalling pathways, such as the hedgehog pathway. To identify the mutations, we are sequencing candidate genes and are using whole-genome sequencing.

Poster Ref: P1-A-020

Theme: A: Development

The polarity complex protein Scribble regulates myelination and remyelination in the CNS.

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The development and regeneration of myelin by oligodendrocytes requires the induction of intracellular polarization. This regulates the directed migration of oligodendrocyte progenitor cells (OPCs) towards developing white matter tracts or demyelinated lesions and the maturation of initial oligo-axonal contacts into nascent myelin sheaths. Polarity complex proteins are evolutionarily-conserved regulators of intracellular polarity whose role in oligodendrocytes is unknown. Scribble is expressed throughout oligodendroglial development, and is upregulated in mature oligodendrocytes where it is localized to both developing and mature CNS myelin sheaths. Knockdown of Scribble expression in cultured oligodendroglia results in disrupted OPC morphology and migration and myelination initiation. When Scribble expression is conditionally eliminated in the myelinating glia of transgenic mice, myelin initiation in CNS is disrupted both during development and following focal demyelination, longitudinal extension of the myelin sheath is disrupted, and normal domain organization surrounding the node of Ranvier is lost. Once myelin is initiated, however, Scribble acts to negatively regulate myelin thickness by modulating activation of the ERK/MAP kinase pathway. These findings indicate that a better understanding of polarity signalling in oligodendrocytes is of great potential importance for developing novel therapies targeting all stages of the remyelination process.

Theme B: Molecular, Cellular and Synaptic Mechanisms

Posters P1-B-001 to P1-B-043

Poster Ref: P1-B-001

Theme: B: Molecular, Cellular and Synaptic Mechanisms

In-vitro models utilised to enhance our understanding of early mechanisms of misfolded protein formation, accumulation and clearance.

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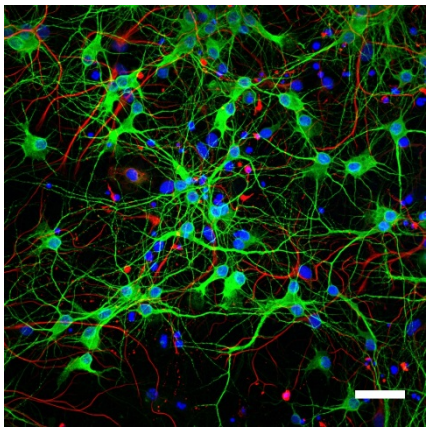
The relationship between misfolded prion protein (PrP), infection and neurotoxicity is still not clearly understood. Previous work from our group demonstrated that inoculation of refolded recombinant PrP into transgenic mice expressing a proline to leucine mutation at PrP codon 101 (101LL) resulted in the presence and seeding of PrP amyloid plaques in the brain in the absence of prion disease or replication of infectivity. Subsequent subpassages produced further amyloid seeding but no disease. Here we demonstrate clearly that abnormal forms of PrP can exist in the brain without causing prion disease. PrP misfolding can also be separated from propagation of prion infectivity as PrP amyloid accumulation can be induced in 101LL transgenic mice in the absence of infected inoculum. Interestingly throughout these experiments we observed that WT control mice were all negative for plaque deposition post inoculation. We could therefore hypothesise that in the absence of this point mutation the healthy brain can maintain homeostasis and efficiently clear any abnormal protein present. Further analysis of these intricate mechanisms is crucial to fully understand amyloid interactions within a healthy brain and whether elements such as age for example would be an important factor regarding homeostasis. To address these issues our investigations focus primarily on early time point mechanisms of cellular response after challenge with fluorescently labelled amyloid fibrils in both WT and 101LL models utilising both *in vivo* and *in vitro* models. We have currently developed two *in vitro* systems one with primary hippocampal/glial cells isolated from E17 embryos and the second using organotypic brain slices. These systems are in the process of optimisation and will provide easily assessable models for investigating the trafficking and interactions of fluorescently labelled misfolded protein *in vitro*.



Confocal image displaying the intricate complexity of primary hippocampal neuronal cells isolated from Day 17 mouse embryos. Growing these cultures *in vitro* allows for a highly controlled, easily accessible model for studying protein interactions at a cellular level. This image is stained with the neuronal marker MAP2 (green), astrocyte marker GFAP (red), and nuclei marker DAPI (blue).

Poster Ref: P1-B-002

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Different roles for β-arrestin2 in morphine analgesia and reinforcement.

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Mu opioid receptors (MOPrs) in pain sensing dorsal root ganglion (DRG) neurones contribute to morphine analgesia. Morphine also stimulates reward/reinforcement possibly through disinhibition of dopaminergic neurones in the ventral tegmental area (VTA), an effect implicated in its abuse and dependence. We hope to achieve sustained analgesia without affecting reward by exploiting differential MOPr signalling mechanisms in DRG and VTA neurones. According to the literature MOPrs, δ receptors (DOPrs) and β-arrestin2 (β-arr2) are all necessary components of the signalling complex in nociceptive neurones for morphine analgesic tolerance.

We are examining whether disruption of this complex produces sustained analgesia with or without perturbing reward by studying wild type (C57Bl/6) mice and mice lacking one (+/-) or both (-/-) alleles encoding MOPrs, DOPrs and β-arr2. Whole-cell voltage-clamp recordings from cultured DRG neurones of MOPr+/- and MOPr-/- mice confirm the necessity for MOPrs in morphine-evoked inhibition of VACCs. Morphine did not prolong MOPr-/- mouse tail withdrawal from noxious heat and had a reduced potency in MOPr+/- mice. The latter were more prone to morphine analgesic tolerance (10 mg/Kg for 10 days) than were WT mice. By contrast, β-arr2+/- and β-arr2-/- mice exhibited normal morphine analgesia but did not develop significant morphine tolerance. β-arr2-/-mice show prolonged basal tail withdrawal latency and this is caused by increased constitutive MOPr signalling. Morphine caused negligible inhibition of GABAergic IPSCs in VTA neurones of MOPr-/- mice and was less potent in this regard in MOPr+/- neurones. A lack of β-arr2 caused an unexpected reduction in morphine's inhibition of IPSCs in VTA neurones and a reduction in morphine stimulation of locomotor activity, without altering morphine conditioned place preference (CPP). Morphine stimulated locomotor activity and CPP were reduced and absent in MOPr+/- and MOPr-/- mice, respectively. Experiments with DOPr-/- and β-arr2-/-/DOPr-/- mice are ongoing.

It would be advantageous to achieve sustained MOPr signalling in the pain pathway without stimulating reward. This may be possible by exploiting differences in the signalling mechanisms in the reward and pain pathways.

Poster Ref: P1-B-003

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Investigating the role of Oxr1 in mitochondria.

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There is considerable evidence that oxidative stress (OS) is a crucial factor in aging and aging-related neurodegenerative diseases. Therefore, it is important to understand how neurons respond to, and counteract OS. Oxidation resistance 1 (Oxr1) is considered as an important oxidative stress sensor in neuronal cells and it is known to play a protective role against OS-induced neurodegeneration. However, the function of Oxr1 is not known and the significance of its mitochondrial localisation has not been investigated. In brief, the aim of my project is to understand the role of Oxr1 in mitochondria. I report that Oxr1 isoforms have different specific cellular localisations and those isoforms that are mitochondrially localised are likely to be membrane bound. In order to investigate the relative neuroprotective activity of Oxr1 in the cytoplasm versus the mitochondria, Oxr1 constructs fused with specific localisation signals were generated. Cellular survival and mitochondrial morphological changes were studied. Upon oxidant insult, cytoplasmic Oxr1 exhibited stronger protection against oxidative stress than the mitochondrially localised protein and both cytoplasmic and mitochondrially localised Oxr1 was able to prevent oxidative stress induced structural alternations. To determine whether a lack of Oxr1 *in vivo* can lead to alternations in mitochondrial function, oxygen consumption levels, mitochondrial morphology, mitochondrial complex activities and membrane potential were measured from primary cerebellar granule cells in Bella (Oxr1 deletion) mice, which indicated that mitochondrial dysfunction is not likely to occur prior to the establishment of apoptosis in the cerebellum of these mutants. Such findings deepen our understanding of Oxr1 and provide further evidence of Oxr1 as an anti-oxidative stress regulator.

Poster Ref: P1-B-004

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Characterisation of leptin mimetic agents for the treatment of Alzheimer**'s disease.**

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Leptin modulates excitatory synaptic transmission and synaptic plasticity in the hippocampal CA1 region (Harvey 2007). Recent evidence suggests the leptin system is a potential therapeutic target in Alzheimer's disease as leptin prevents the aberrant effects of Aβ on hippocampal synaptic function. Since leptin has many roles in the CNS and periphery it is not a suitable drug to be used for treatment therefore several bioactive leptin fragments have been synthesized (Grasso et al; 2001). Of the commercially available bioactive fragments, leptin (116-130) is thought to be the most potent whereas leptin (22-56) is less active (Grasso et al; 1997). As leptin has cognitive enhancing properties, here we have tested the cognitive enhancing effects of both leptin (116-130) and leptin (22-56) on hippocampal LTP using standard extracellular recordings. In brief, parasagittal hippocampal slices (300μm) from juvenile Sprague-Dawley rats (11- 24 days old) were used. Fibers of the Schaffer collateral-commissural pathway were stimulated at 0.0333Hz and extracellular field excitatory postsynaptic potentials (fEPSPs) recorded. In order to examine if leptin and leptin (116-130) potentiate LTP, a theta burst stimulation (TBS) protocol (5 trains of 8 stimuli; 100Hz with 200ms intervals) was used in slices treated with leptin or leptin (116-130) (both at 50nM; 50min) which resulted in 157 ± 6.6% ($n=4$; $p<0.05$) and 144 ± 6.5% ($n=4$; $p<0.05$) increase in synaptic transmission respectively compared to baseline. However leptin (22-56; 50nM; 50min) failed to increase synaptic transmission ($n= 4$; $p> 0.05$). AMPA receptor trafficking plays a crucial role in hippocampal synaptic plasticity and leptin increases GluA1 trafficking to synapses (Moult et al; 2010). In this study, application of either leptin or leptin (116-130) (both at 50nM; 15min) increased surface GluA1 labelling to 140 ± 0.5% ($n=9$; $p< 0.05$) and 125 ± 0.4% ($n=9$; $p< 0.05$) respectively compared to control in hippocampal neurons. However neurons treated with leptin (22-56) failed to show increased GluA1 surface expression (98 ± 0.4% of control; $n=9$; $p> 0.05$). In conclusion, these data show that leptin (116-130) mimics the cognitive enhancing effects of leptin.

Poster Ref: P1-B-005

Theme: B: Molecular, Cellular and Synaptic Mechanisms

The neostriatum: two neuronal networks without direct interaction.

Violeta Lopez-Huerta[1], Yoko Nakano[1], Johannes Bausenwein[1], Omar Jaidar[1], Michael Lazarus[2], Yoan Cherassse[2], Marianela Garcia-Munoz[1] and Gordon Arbuthnott[1]

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Neostriatum is known to have a large neuronal network of high acetylcholine esterase activity (AChE) that configure the matrix compartment and a smaller set of neurons poorly stained for AChE that form the striosome compartment. In spite of much knowledge accumulated about these two compartments how they interact has been a matter of speculation. We tested this question by selective manipulation of neurons in the matrix.

We performed whole cell patch-clamp recordings on sagittal slices (250 µm) following unilateral stereotaxic injections of AAV1-dflox-hChR2-mCherry, AAV10-Syn-ChR2-mCherry or AAV10-syn-hM3Di-mCherry in neostriatum. Two weeks post-surgery were allowed for virus expression. Synaptic events were evoked by photostimulation or glutamate puff (1mM/20psi/50ms). Additionally we trained mice for single-pellet reach-to-grasp task following procedures as established by Marques, J.M. & Olsson, I.A. (2010) J. Neuroscience Methods, 193, 82-85. The inert hM3di-agonist clozapine-n-oxide (CNO, 3mg/kg i.p.) was administered for 3 consecutive days. We carried out conventional histological processing and immunofluorescence against MOR1.

Findings: 1-Adeno-associate virus serotype rh10 (AAV10) expresses in striatal neurons located in matrix compartment sparing most neurons in striosomes and including all striatal interneuron subtypes. This selective expression allowed photoactivation of matrix compartment and patch clamp recordings of neurons belonging to both networks. 2-We observed absence of physiological synaptic connections to neurons in striosomes from neurons in matrix and vice versa. 3- Selective matrix inhibition by expression (designer receptors exclusively activated by a designer drug) DREADD hM3di and DREADD agonist clozapine-n-oxide decreased performance of a learned reach to grasp motor task. Considering the absence of direct matrix-striosome communication the striosome function needs to be addressed. Striatal outputs from matrix are directed to substantia nigra reticulata and thalamus whereas striosome output ends mainly in substantia nigra compacta, from where striosomes could modify diffuse extracellular fluctuations of dopamine and exert a modulatory tone on striatal neuronal excitability.

Poster Ref: P1-B-006

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Cholinergic interneuron sprouting in striatum.

Gordon Arbuthnott, Nilupaer Abudukeyoumu , Marianela Garcia-Munoz, Yoko Nakano and Omar Jáidar
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Large intrinsic interneurons are the source of acetylcholine (ACh) in striatum. In spite of comprising only 1-3% of all striatal neurons they have widespread connections and produce one of the highest concentrations of ACh in the brain. Cholinergic interneurons have important postsynaptic and presynaptic modulatory functions that impact the duration, strength and pattern of striatal output neurons. Here we report the use immunotoxin ribosome inactivating protein (saporin) associated to choline acetyltransferase (ChAT) to selectively damage striatal cholinergic interneurons. All our experiments complied with guiding policies and principles for experimental procedures endorsed by the government of Japan. We used bacterial artificial chromosome (BAC) transgenic mice D1-eGFP or D2-eGFP. Anti-ChAT-SAP (300nl) was delivered ipsilaterally on the left striatum of approximately 21 days old mice. At least two weeks were allowed for viral expression before anatomical confirmation of cell loss was performed. Mice were intracardially perfused, brains were postfixed for at least 2h and then cryoprotected in sucrose. Sections were cut at 60µm, and neuronal cell bodies were identified with anti-choline acetyltransferase (ChAT) and axons with anti-vesicular Ach transporter (vAChT). Alternate sections were incubated overnight with anti-vAChT (rabbit polyclonal 1:1000, Synaptic Systems, Germany) or with anti-ChAT (goat polyclonal 1:100, Millipore) at 4°C and stained with donkey secondary antibodies. Stained mounted sections on slides were inspected using a spinning disc confocal microscope (Olympus BX-DSU) and confocal microscope (Carl Zeiss LSM780). Pictures were taken using Neurolucida software or ZEN software and a Hamamatsu camera (EM-CCD C91). The cholinergic system is still developing in these young mice and vAChT positive terminals (counted stereologically) increase over the measurement time. Nonetheless the first week post injection, counts of terminals in the damaged striatum increase more than controls and remain elevated even though the number of ChAT positive cells remain low over five weeks after toxin injection. Whether these changes are due to terminal sprouting of cholinergic interneurons or brainstem cholinergic input remains to be determined.

Poster Ref: P1-B-007

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Determination of the contribution of TRAK1 and TRAK2 kinesin adaptor proteins in axonal and dendritic mitochondrial trafficking.

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UCL School of Pharmacy

Neuronal function requires regulated anterograde and retrograde trafficking of mitochondria along microtubules using the molecular motors, kinesin and dynein, to ensure supplies of energy in the form of ATP for synaptic transmission. Previous work has established that the kinesin adaptor proteins, TRAK1 and TRAK2, play an important role in mitochondrial transport in neurons. They link mitochondria to kinesin motor proteins *via* a TRAK acceptor protein in the mitochondrial outer membrane, the Rho GTPase, Miro. In addition, both TRAKs associate with the post-translational modification enzyme, O-linked N-acetylglucosamine transferase (OGT). Thus, TRAK1 and TRAK2 form quaternary, mitochondrial trafficking complexes composed of TRAK1 or TRAK2, kinesin heavy chain, OGT and Miro. Down-regulation of TRAK1 or TRAK2 expression as well as dissociation of the quaternary complex by a TRAK dominant negative construct both impaired mitochondrial transport in axons of hippocampal neurons in culture1.

Recent studies found that TRAK1 preferentially controls mitochondrial transport in axons of hippocampal neurons by virtue of its binding to both kinesin and dynein motor proteins whereas TRAK2 controls mitochondrial transport in dendrites due to its binding to dynein. However, it is not clear whether the function of any of these proteins is exclusive to axons or dendrites and if their mechanisms of action are conserved between different neuronal populations. Therefore here, we have determined TRAK1 and TRAK2 distribution and in conjunction, the effect of TRAK1 and TRAK2 gene knock-down in axons and dendrites of both primary hippocampal and cortical neurons to evaluate their respective contribution to axonal and dendritic mitochondrial trafficking. These studies will help to elucidate the mechanisms regulating the molecular interplay between mitochondrial transport and energy supply in cultured neurons and may advance our understanding of neurodegenerative disorders in which defects in mitochondrial transport are implicated.

Supported by the BBSRC (UK).

1.Brickley, K. and Stephenson, F.A. (2011) J. Biol. Chem. 286, 18079.

Poster Ref: P1-B-008

Theme: B: Molecular, Cellular and Synaptic Mechanisms

The dissociation of the N- and C-terminal fragments of latrophilin-1 caused by perfluorooctanoic acid (PFOA) impairs acetylcholine release at the mouse neuromuscular junction.

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Perfluorooctanoic acid (PFOA) is a synthetic surfactant and pollutant belonging to the perfluorinated compound (PFC) family, with many industrial applications. Since the detection of PFCs accumulation in human tissues, their effects on physiological functions have been investigated. *In vitro*, exposure to >200 μM PFCs increases the level of necrosis and apoptosis in neuroblastoma cells and disrupts calcium homeostasis in hippocampal neurons, and 10-30 μM are sufficient to induce changes in Purkinje cells membrane potentials. Neonatal exposure to 21 μM/kg body weight alters the expression of proteins involved in neuronal growth and synaptogenesis, and can induce immunotoxicity similar to that observed in neurodevelopmental disorders.

Here we study the effect of PFOA on the release of neurotransmitter regulated by latrophilin-1 (LPHN1), an adhesion G protein-coupled receptor involved in modulating spontaneous exocytosis. We show that the exposure of neuroblastoma cells expressing LPHN1 to 100 μM PFOA causes the dissociation of the N and C-terminal fragments (N/CTF) of LPHN1, although both fragments remain on the cell surface. At concentrations above 4.8 mM (0.2%), PFOA differentially solubilises the NTF and then (at 1%) also the CTF.

The physiological effects of LPHN1 dissociation were assessed by measuring the frequency of quantal acetylcholine release at mouse neuromuscular preparations induced by LTXN4C, the non-pore-forming mutant of α-latrotoxin. Under control conditions, LTXN4C caused a 100-200 fold increase in the frequency of miniature events, and this effect was mediated by LPHN1. In a dose-dependent manner, PFOA inhibited, and at 100 μM completely blocked, the toxin-evoked exocytosis. PFOA also perturbed depolarisation-induced acetylcholine release. These results indicate that the dissociation of the two fragments of LPHN1 by PFOA prevents their interaction and receptor signalling, which is involved in the regulation of calcium influx and exocytosis.

Poster Ref: P1-B-009

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Hebbian and homeostatic plasticity mechanisms differentially modify RS and IB cell output in layer V of the mouse barrel cortex *in vivo*.

Stuart Greenhill and Kevin Fox

Cardiff University

Previous studies in our lab have shown that, in the rat barrel cortex, regular spiking (RS) and intrinsic bursting (IB) cells respond differently to whisker deprivation; RS cells show depression of deprived whisker stimulation and an increase in spike timing fidelity, while IB cells do not depress but instead show potentiation of responses to spared whisker stimulation (Jacob et al, Neuron 73, 391-404 (2012)). We first tested whether these results generalised to the mouse barrel cortex, and then investigated the molecular substrate of any observed plasticity through the use of two mutant strains.

Sharp electrode intracellular recordings were made from acutely anaesthetised preparations of both naive mice and mice whose D-row whiskers had been unilaterally clipped for either 3 or 10 days. The D1-D3 barrels were localised before recording using intrinsic optical imaging at 700nm to guide recordings. Upon penetration and electrophysiological classification of a layer V pyramidal cell, the receptive field and whisker evoked activity of the cell was automatically mapped using a 3x3 piezo matrix stimulator. Cells were classified as RS or IB depending on their response to depolarising current.

In wild-type mice (C57BL/6J), RS cells in layer V showed a depression in firing rates (to 71% of control) in response to both principal (deprived) and surround (spared) whisker stimulation after 3 days, with some recovery of responses after 10 days D-row spared deprivation. In contrast, IB cells displayed spike-rate potentiation (to 212% of control) across all vibrissae types, but only after 10 days of deprivation. In TNF-alpha KO mice, RS cells displayed depression similar to that of wild types after 3 days, but showed no rebound at 10 days, suggesting a homeostatic mechanism of recovery. In mice lacking autophosphorylating alpha-CaMKII (T286A mice), RS cells displayed similar phenotypes to WT mice after 10 days, suggesting Hebbian-like plasticity is not involved in recovery. IB cells displayed a phenotype that relied on both plasticity pathways. We conclude that RS and IB cells require different modes of plasticity to alter their supratheshold activity in response to whisker deprivation.

Poster Ref: P1-B-010

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Acute and chronic effects of transient mutant DISC1 on layer II/III neurons in layer 2/3 mouse barrel cortex.

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DISC1 has been implicated in schizophrenia and has an important role in brain development. We used a transgenic mouse with a dominant negative fragment of the DISC1 c-terminal (DISC1-cc), activated for 24-48 hours by injection of tamoxifen. Activation of the mutant protein at P7 results in schizophrenic like behaviour (Li et al, 2007) and a loss of experience dependent plasticity in layer 2/3 adult barrel cortex, while activation of DISC1-cc at P28 has no effect on experience dependent plasticity.

We compared dendritic development in WTs and DISC1s and showed that in WTs, dendritic structure was largely mature by P11. We found that dendritic growth was attenuated in DISC1s at P11 and P14 (both $p<0.05$) but had recovered by P21. Retardation was observed both in basal and apical dendrites. Additionally we measured spine density on characterised dendrites from recorded neurons to look at both acute and chronic effects of mutant DISC1. We also measured short term plasticity of layer 4 inputs to layer 2/3 neurons and found a similar developmental profile to the dendritic growth in WTs while in DISC1 mutants there was a similar retardation in the development of short term plasticity to that found in the dendrites. Action potential firing properties of neurons were also affected by DISC1, with largest effects observed acutely.

To further investigate functional effects of DISC1, we recorded mEPSPs at P8, P14 and P28 and found there to be little effect of mutant DISC1 on mEPSP amplitude or frequency at any age (all $p>0.05$). We also recorded mIPSCs to assess whether inhibition was also affected by mutant DISC1 and found there to be again no significant effects ($p>0.05$).

We measured levels of LTP and LTD in adult mice (P50-P70) given transient expression of mutant DISC1 and in wild type littermates. We found that LTP was entirely occluded in the mutant DISC1s (comparison with WT, $p<0.05$) and that LTD was also reduced in mutant DISC1s. We also found there to be a significant difference between NMDA/AMPA ratios of WTs and DISC1s at P28 and P50 but not at P14. Thus it would seem that transient expression of mutant DISC1 can have acute effects on the neurons which in turn have chronic implications.

Poster Ref: P1-B-011

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Analysing the role of Sox2 in regulating Schwann cell myelination during development and after injury.

Sheridan Roberts

University of Plymouth

Sox2 is a member of the SRY-related HMG box (SOX) family of transcription factors and is best known for its ability to regulate cell proliferation and pluripotency. In the peripheral nervous system (PNS), Sox2 is expressed in the nuclei of immature Schwann cells prior to myelination and is down-regulated as Schwann cells begin to myelinate. Using a Schwann cell specific CRE line together with a Sox2-IRES-GFP transgenic mouse line that expresses Sox2 and GFP following recombination, we have fully tested the effects of maintaining Sox2 expression in Schwann cells during development. Our data shows that both at early post-natal time points and into adulthood, Sox2 triggers Schwann cell proliferation, represses myelination and reduces motor function *in vivo*.

Following nerve injury, Schwann cells have been shown to re-express Sox2, down-regulate myelin proteins and adopt a repair-supportive phenotype, to facilitate axonal regeneration and functional repair. Once nerve regeneration and repair is complete, Sox2 expression is again reduced and Schwann cells differentiate back into myelinating Schwann cells. We wanted to analyse the effects of maintaining Sox2 expression in Schwann cells following peripheral nerve injury. Using the same transgenic mouse line, we were able to show that maintained Sox2 expression following injury resulted in an increase in proliferation, reduced myelin protein expression and a reduction in functional recovery 21 days post injury. We are now analysing whether Sox2 expression in Schwann cells alters the conduction velocity of the sciatic nerve, as well as sensory function so that we can further characterise the effects of Sox2 expression in Schwann cell development and disease.

Poster Ref: P1-B-012

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Increased polygene scores for schizophrenia are associated with altered surface area and gyrification in a cohort at familial high risk of developing schizophrenia.

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Introduction: Schizophrenia is a highly heritable psychiatric disorder characterized by both global and regional brain alterations that precede disorder onset. It is currently unclear to what extent these brain alterations are related to an underlying genetic disposition to develop schizophrenia, and whether different cortical parameters are differentially affected by a genetic loading for schizophrenia. We have therefore investigated whether a polygenic risk score of known genetic risk variants for schizophrenia is associated with cortical surface area, thickness and gyrification in a cohort at familial high risk for the disorder.

Methods: Unaffected high risk individuals aged 16-25 years were recruited on the basis that they had at least two first- or second-degree relatives affected with schizophrenia. Polygenic risk profiles were created using summary data from the most recent PGC GWAS of schizophrenia. These scores are calculated by taking weighted sum of schizophrenia-associated alleles across the genome and thus reflect an individuals genetic load for schizophrenia. Freesurfer was used to derive global and frontal and temporal values of cortical thickness, surface area and gyrification. All statistical analysis was performed with R.

Results: There was a significant effect of polygene score on global left surface area ($t = 2.037$, $df = 1,66$, $p = 0.046$), as well as on left ($t = 2.44$, $df = 1,66$, $p = 0.0174$) and right frontal surface area ($t = 2.101$, $df = 0.0395$). There was also a significant effect of polygene score on left frontal gyrification ($t = 2.910$, $df = 1,66$, $p = 0.00492$), and right frontal gyrification ($t = 2,519$, $df = 1,66$, $p = 0.0142$). No significant effects for the temporal lobe emerged, nor for any of the cortical thickness values.

Discussion: Our findings suggest that a higher genetic loading for schizophrenia is associated with increased surface area and gyrification, but not cortical thickness. As surface area and gyrification are determined early in fetal life, our findings suggest that an increased genetic loading for schizophrenia is associated with a neurodevelopmental brain disruption to processes affecting surface area and gyrification, but not thickness.

Poster Ref: P1-B-013

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Pharmacologically induced theta (4-7 Hz) and gamma (30-80 Hz) oscillations in layer V of the rat primary motor cortex *in vitro*.

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Understanding neuronal network dynamics in primary motor cortex is highly important in the context of recent research implicating this region in the aetiology of Parkinson's disease. Previous work in this laboratory demonstrated beta oscillatory activity (15-29 Hz) in coronal slices in rat primary motor cortex (M1, Yamawaki *et al.*, 2008). Here, we used local field potential recording to investigate neuronal network oscillatory activity in sagittal slices (450 µm) containing M1 prepared from adult (50-100g) Wistar rats and maintained *in vitro*. Application of kainic acid (100-150 nM) and carbachol (5-10 µM) induced simultaneous oscillations at 6.6 ± 0.1 Hz and 36.5 ± 0.4 Hz, which we term theta and gamma oscillations, respectively. Using cross-frequency coupling and bicoherence analysis we determined that these oscillations were not coupled by frequency or amplitude. We investigated mechanisms underlying these oscillations using a pharmacological approach. Blockade of GABA-A receptors with the specific antagonist, gabazine, at 250 nM resulted in an increase in theta power by 47.9 ± 10.2%, and application of a higher concentration (2 µM) further increased theta power by 81.0 ± 11.6%. Application of the specific AMPA receptor blocker SYM2206 (20 µM) induced an increase in theta power and subsequent blockade of gap-junctions with carbenoxolone caused a decrease in theta activity. Together, these data indicate a non-synaptic origin for theta oscillations. By contrast, application of gabazine at 250 nM reduced mean peak gamma power by 71.8 ± 6.5%, and a higher concentration (2 µM) abolished all gamma activity. Blockade of AMPA receptors with SYM2206 also abolished gamma activity, indicating that fast oscillations in M1 depend on both excitatory and inhibitory synaptic transmission. These data show that deep layers of rodent M1 *in vitro* display independent synaptic and non-synaptic modes of oscillatory activity, suggesting co-existence of multiple mechanisms of rhythm generation in the sagittal slice preparation.

Yamawaki N, Stanford IM, Hall SD, Woodhall GL. (2008) Pharmacologically induced and stimulus evoked rhythmic neuronal oscillatory activity in the primary motor cortex *in vitro*. Neuroscience. 151(2):386-95.

Poster Ref: P1-B-014

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Pharmacologically induced persistent gamma (30-80Hz) oscillations in layer II of the rat piriform cortex *in vitro*.

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The piriform cortex (PC) is a phylogenetically old, trilaminate structure, whose functions include olfactory processing and memory consolidation. The PC is also thought to play a key role in the development of epilepsy (epileptogenesis). PC gamma oscillations have been studied in both anaesthetised and awake rodents *in vivo*; however, to date they have not been reported *in vitro*. We demonstrate that application of kainic acid and carbachol induced persistent gamma oscillations in the PC in an *in vitro* brain slice preparation from 80-100 g male Wistar rats. Local field potential recordings of neuronal network oscillations were made in coronal slices of PC (450 µm) and their pharmacology investigated to determine underlying mechanisms. Gamma oscillations in layer II of the PC were induced with a mean (± SEM) frequency of 35.93 ± 0.42 Hz and power of 44.87 ± 4.05 µV^2 (n = 120 slices). Blockade of GABAA receptors using gabazine (250 nM/2 µM) reduced mean peak gamma power by 67 ± 3.98% ($p<0.01$) and 86.54 ± 2.77% ($p<0.01$) respectively. Selective AMPA receptor blockade using SYM2206 (20 µM) reduced gamma peak by 86.32 ± 3.9% ($p<0.01$). Gap junction blockade with carbenoxolone (200 µM) reduced gamma peak by 90.85 ± 2.7%. Blockade of NMDA and GABAB receptors had no effect on γ oscillations. Dependence on AMPA and GABAA receptors and gap junctions implies the oscillations are synaptic and rely on inhibitory transmission for pacing. The ability to induce gamma oscillations *in vitro* will allow investigation of changes in neuronal network activity during epileptogenesis.

Poster Ref: P1-B-015

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Effects of synaptically activated spikes on plasticity of the mouse corticostriatal synapse.

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Activity-dependent synaptic plasticity is a probable mechanism for learning and memory in the brain. Here, we report our study of synaptic plasticity in the corticostriatal pathway. As in other brain regions, synaptic plasticity in this pathway depends on precise timing of presynaptic inputs and postsynaptic outputs. Previous studies of this spike-timing dependent plasticity (STDP) in the corticostriatal pathway used somatic current injection to cause postsynaptic firing and showed LTP and LTD depending on the relative timing of inputs and outputs. We are interested in how induction of postsynaptic spikes by synaptic inputs might alter STDP properties.

We made *in vitro* patch-clamp recordings of spiny projection neurons (SPNs) in the dorsomedial striatum. We found that synaptically activated spikes differ from somatically evoked spikes in certain measures and are associated with a different spectrum of STDP. Synaptically evoked spikes had significantly lower spiking threshold, peak amplitude, spike height and spike half width, whereas rise time was significantly higher than somatically activated spikes. These differences could be reproduced in a computational model. To test whether these differences in firing properties were reflected in plasticity, we developed a presynaptic STDP protocol using synaptic inputs to control firing. This new protocol exhibited an overall LTD for both positive and negative intervals between presynaptic and postsynaptic spikes.

In summary, our work demonstrated differences in the characteristics of synaptically activated spikes and corresponding differences in synaptic plasticity in the corticostriatal pathway.

Poster Ref: P1-B-016

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Pharmacologically induced neuronal network oscillations at delta frequency (2-4 Hz) in layer V of the rat primary motor cortex *in vitro*.

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The sleep-wake cycle is characterised by complex oscillatory activity with different patterns and neurochemical mechanisms. Low amplitude, fast oscillations are observed in rapid eye movement (REM) sleep, whereas non-REM, deep sleep stages (NREM3 & NREM4) are characterised by high amplitude slow (delta) waves (2-4 Hz). Delta oscillations are thought to play a crucial role in physiological processes such as memory consolidation and in the pathological states such as Alzheimer`s disease, but the basic neurobiology of the rhythm is relatively poorly understood. The current study investigates the mechanisms underlying the basis of the motor cortical delta rhythm *in vitro*, and compares the incidence of the rhythm in deep and superficial layers of primary motor cortex (M1). Extracellular (local field potential; LFP) recordings were obtained from sagittal brain slice (450 µm) preparations from male Wistar rats (50-100 g). A slow transition from fast (theta-gamma) oscillations to slow oscillations (delta) was identified such that, in conditions of low cholinergic and dopaminergic tone, pharmacologically evoked gamma (34-40 Hz) and theta (7-14 Hz) oscillations gradually shifted to beta (25-29 Hz) and slow theta (5-7 Hz) oscillations, before a high amplitude (~300 µV2) delta rhythm emerged with a frequency range of 2-4 Hz. To our knowledge, this is the first demonstration of a motor cortical delta rhythm *in vitro*. Preliminary pharmacology suggests the involvement of GABA-A, GABA-B, AMPA, KA and mAch receptors in generating the M1 delta rhythm. Unlike a previous report of delta activity in rodent secondary somatosensory (S2) cortex *in vitro* (Carracedo *et al.*, 2013), NMDA receptors did not appear to be involved in delta activity in M1. Investigations using multiple recording sites suggest deep layers of M1 to be the origin of the delta rhythm. Further experiments will investigate the role of different neuronal subtypes in generation of delta activity in M1.

Carracedo LM, Kjeldsen H, Cunnington L, Jenkins A, Schofield I, Cunningham MO, Davies CH, Traub RD, Whittington MA. (2013) A neocortical delta rhythm facilitates reciprocal interlaminar interactions *via* nested theta rhythms. J Neurosci. 33(26):10750-61.

Poster Ref: P1-B-017

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Regulation of vesicle trafficking by DISC1: a live cell imaging approach.

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The multifunctional scaffold protein Disrupted-In-Schizophrenia 1 (DISC1) is a risk factor for psychiatric disorders including major depression, bipolar disorder and schizophrenia. DISC1 is involved in many biological processes of central importance for neuronal development and function, including organelle trafficking. In axons, DISC1 regulates mitochondrial movement, a function that is likely mediated by its association with Trafficking-Protein-Kinesin-binding-1 (TRAK1), a protein that links mitochondria to kinesin and dynein for microtubule-based trafficking. TRAK1 is involved in trafficking of additional cargoes, including endosomes and GABAa-containing vesicles, suggesting that the trafficking function of DISC1 may also extend beyond mitochondria. To test this hypothesis, we expressed surface protein X labelled with the basic fluorescent protein mKate2 or the photoconvertible fluorescent protein Dendra2 in primary mouse hippocampal neurons to directly assess the motility of protein X-containing vesicles in axons and dendrites, respectively. Axonal vesicle trafficking was visualised by wide-field time lapse imaging, while dendritic trafficking was assessed by live confocal time lapse imaging after photoconversion of a small region within the dendrite, coupled with a novel bespoke image analysis method. We observed that, in axons, X-mKate is transported in large fast-moving vesicles that predominantly travel in the retrograde direction. Expression of human DISC1, but not the potentially disease-related variants DISC1-37W or DISC1-607F, markedly increases movement of axonal fluorescent X-containing vesicles in the anterograde direction, without affecting their total motility. In dendrites, smaller vesicles containing X-Dendra2 travel bidirectionally from the photoconversion region. Consistently with what was observed in axons, DISC1 expression promotes the movement of X-Dendra2-expressing vesicles towards the distal portion of dendrites. These observations suggest for the first time the potential involvement of DISC1 in the regulation of intracellular trafficking of surface protein-carrying vesicles in neurons, with a possible modifying effect of candidate disease-related DISC1 variants.

Poster Ref: P1-B-018

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Metabolic cost of action potentials in MNTB neurons is altered by activity-dependent NO modulation.

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The nervous system consumes a substantial proportion of the energy produced by the full body (Harris *et al.*, 2012). Much of this energy consumption results from Na+ entering a neuron to produce action potentials (AP), which then needs to be pumped out again by the Na/K-ATPase, consuming ATP.

In parallel to metabolic requirements, a lot of control mechanisms act to tune ion channel activity to neuronal function. In particular, nitric oxide (NO) modulates target neuron excitability (Na+ channels) and switches the AP repolarization from Kv3 to Kv2 potassium channels (Steinert *et al.*, 2011). This change also increases the neuronal maximal frequency firing in MNTB neurons in the auditory brainstem.

The aim of this work to is increase our understanding of the relationship between neuromodulation and the metabolic cost of neural activity. We have built a computational model of MNTB auditory brainstem neurons, taking account of their modulation by NO, and describing the glycolysis and mitochondrial activity in response to ATP demands from the Na/K-ATPase following an AP (Cloutier and Wellstead, 2010). Model outputs are compared between (1) the baseline (control) condition, (2) following increased NO levels, and (3) in other hypothetical conditions that allow examination of the contribution of particular ion channel types.

NO modulation reduces postsynaptic AP failures during high frequency stimulation, by potentiation of the Kv2 channels (Steinert *et al.*, 2011). Our results show this is metabolically costly, but also that the parallel down-regulation of Na channels decreases the global metabolic cost. In addition, the model demonstrates that reduction of all ion channel densities can increase metabolic efficiency while still allowing AP generation.

Cloutier, M., Wellstead, P., 2010. The control systems structures of energy metabolism. J. R. Soc. Interface R. Soc. 7, 651–665.

Harris, J.J., Jolivet, R., Attwell, D., 2012. Synaptic energy use and supply. Neuron 75, 762–777.

Steinert, J.R., Robinson, S.W., Tong, H., Haustein, M.D., Kopp-Scheinpflug, C., Forsythe, I.D., 2011. Nitric oxide is an activity-dependent regulator of target neuron intrinsic excitability. Neuron 71, 291–305.

Poster Ref: P1-B-019

Theme: B: Molecular, Cellular and Synaptic Mechanisms

MSK1 contributes to the cognition-enhancing effects of environmental enrichment.

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Environmental enrichment (EE) of laboratory rodents enhances learning and memory across a variety of behavioural paradigms. In addition, EE imbues in mammals greater resilience to stressful situations, higher resistance to the addictive effects of drugs of abuse and improves recovery in both acquired and neurodegenerative brain injury. As such, considerable interest has arisen in the molecular mechanisms by which EE affects neuronal structure, function and cognition.

We have previously shown that mice mutant for mitogen and stress activated kinase 1 (MSK1) did not display the enhancement of hippocampal synaptic transmission observed in wild-type (WT) mice after EE and showed a blunted increase in spine density [1]. This suggests that MSK1 may transduce at least some of the positive effects of EE into lasting structural and functional neuronal changes. This suggestion is made all the more apposite given 1) that MSK1 is downstream of BDNF-activated TrkB receptors and 2) the ability of MSK1 to regulate gene expression *via* the phosphorylation of both CREB at S133 and histone H3 at S10, all of which have been implicated in mediating the positive effects of EE.

The present work thus investigated whether EE improved hippocampus-dependent spatial reference and working memory in an MSK1-dependent manner. To this end, we reared WT and MSK1 kinase dead (MSK1 KD) mice in standard conditions or EE from birth to 2.5-4 months of age.

Our data show that the kinase activity of MSK1 is required for at least part of the cognitive-enhancing effects of EE: compared to wild-type mice, MSK1 KD mice showed less improvement in hippocampus-dependent spatial working and reference memory as measured by the Spontaneous Alternation and the Water Maze task respectively.

These data suggest that MSK1 is important for converting positive environmental stimulation into enhancements of cognition. Parallel studies of synaptic transmission and plasticity (Privitera *et al*; this meeting) will indicate whether the cellular underpinnings of such enhancements of cognition can be identified.

This work is funded by the BBSRC and WPH.

1. Correa, S.A., *et al.*, MSK1 regulates homeostatic and experience-dependent synaptic plasticity. J Neurosci, 2012. 32 13039-51.

Poster Ref: P1-B-020

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Latrophilin1 regulates store-operated calcium entry in a model neuron system.

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Store-operated calcium entry (SOCE) is a mechanism of inducing calcium influx across the plasma membrane when intracellular calcium stores are depleted. Initially thought to exist in non-excitable cells only for initiating responses to environmental stimuli, SOCE is now known to be almost ubiquitous. The significance of SOCE in neurons has been building in recent years, where it has been shown to play a role in excitability and neurite extension as well as general processes such as regulating gene transcription. However, the role of SOCE in neurotransmitter release at synaptic terminals remains poorly understood.

SOCE activation by latrophilin1 (LPH1), a presynaptic adhesion-G protein coupled receptor, was studied in a murine neuroblastoma cell line (NB2a). These cells develop neuron-like properties with appropriate differentiation treatments. NB2a cells express several SOCE-associated genes: the calcium store sensors stromal interaction molecule 1-2 (STIM1-2), the SOCE channels Orai1-3 and TRPC2, and the SOCE-associated regulatory factor (SARAF). Relative expression analysis by quantitative reverse-transcription PCR showed that stable expression of LPH1 up-regulates STIM2, Orai1-3 and SARAF and differentiation up-regulates Orai3 and TRPC2.

Intracellular calcium recording revealed that both basal calcium influx and thapsigargin-induced SOCE are down-regulated by differentiation in wild-type NB2a but are up-regulated by differentiation in LPH1-expressing NB2a. Furthermore, stimulation of LPH1 by a mutant form of α-Latrotoxin (LTX^N4C), a high-affinity agonist of LPH1, increases SOCE in differentiated cells only. Knock-down of endogenous SOCE proteins has been used to determine the specific downstream proteins in the LPH1 pathway that mediate these effects. These findings demonstrate that LPH1 uses SOCE to modulate calcium signalling in NB2a cells and they further our understanding of LPH1's role at the presynaptic terminal.

Poster Ref: P1-B-021

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Rescuing GluA3 surface expression: subunits and chaperones.

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AMPA receptors are homomeric or heteromeric assemblies of the subunits GluA1 to GluA4. Their functional properties are dependent upon subunit composition and presence and type of auxiliary proteins. We previously showed GluA3 homomeric receptors traffic very poorly to the plasma membrane. Residues Tyr-454 and Arg-461 (in the ligand-binding domain) are responsible for this phenotype: changing these residues to the equivalent in GluA2 (Ala-451 and Gly-458)let the mutant, GluA3(YR/AG), traffic to the plasma membrane similarly to wild-type GluA2. This intracellular retention of GluA3 is not due to the ligand-binding domain instability nor to an inability to form tetrameric assemblies. This suggests that the transport of GluA3 tetramers out of endoplasmic reticulum is blocked, but the molecular explanation is still unclear.

We have now investigated in more detail how GluA3 trafficking may be rescued following expression in a model cell line. Surface expression was either examined directly *via* impermeable biotin labelling and streptavidin pulldown or *via* receptor presence in the soluble supernatant fraction following ultracentrifugation as a proxy readout. Co-expression with wild-type GluA2 subunits significantly improved surface expression of GluA3. However, GluA2 flip gave ~five-fold improvement whereas flop isoform gave ~three-fold. Even co-expression with GluA2(AG/YR) mutant subunit gave two-fold improvement. Unexpectedly, co-expression with stargazin (which promotes trafficking of many AMPA receptor types) did not improve surface expression of GluA3 homomeric receptors. This was not due to lack of interaction, as the proteins showed clear co-association and whole cell current amplitudes of glutamate responses were significantly increased in GluA3 and stargazin co-expressing cells. A possible explanation for poor forward trafficking is that GluA3 tetramers are prone to aggregation. Small chemical chaperones such as 4-phenyl butyrate have been used to rescue misfolded and aggregated proteins. However, whilst GluA3(YR/AG) gave a clear concentration dependent increase in signal, there was no clear effect upon wild-type GluA3 expression. Thus, GluA3 retention is only overcome by heteromeric assembly with another AMPA receptor subunit.

Poster Ref: P1-B-022

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Ataxin-1 CAG expansion during development increases the severity of a mouse model of human spino-cerebellar ataxia type 1, SCA1.

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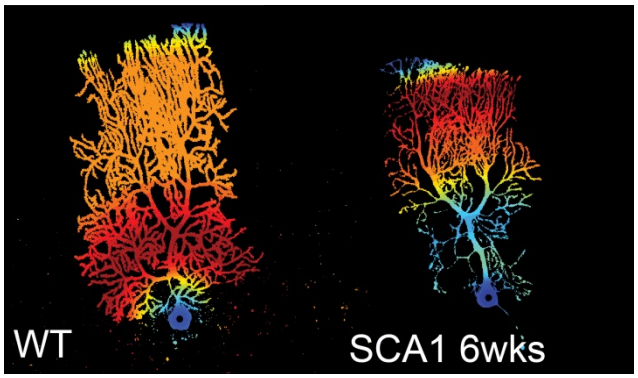
Spino-cerebellar ataxia type 1(SCA1) is a progressive autosomal dominant neurodegenerative motor disorder resulting from a CAG trinucleotide expansion within ataxin-1. In this study, we use a transgenic mouse model of SCA1 where ataxin-1 CAG expansion (82Q) is restricted to cerebellar Purkinje neurons (PNs) and also under doxycycline control. In this mouse doxycycline treatment prevents 82Q expansion and provides an ideal opportunity to determine its functional impact in the developing versus the mature cerebellum.

6 week old SCA1 transgenic mice exhibited motor deficits in the accelerating rotarod test over 5 days ($P<0.05$, two way ANOVA). Their performance and motor learning declined further by 12 weeks of age ($P<0.01$, two way ANOVA). SCA1 mice receiving doxycycline from 0-6 weeks of age exhibited normal motor behaviour at both 6 and 12 weeks of age ($P>0.05$, two way ANOVA), even though in the latter group 82Q expansion occurred for 6 weeks, but from 6-12 weeks of age.

Individually reconstructed PNs from 6 week old SCA1 transgenic mice revealed a reduced complexity of their proximal dendrites in a Scholl analysis ($P<0.01$, one way ANOVA) but similar overall dendritic length compared with controls ($P>0.05$, one way ANOVA). PN dendrites from 12 week old SCA1 mice exhibited a further reduced complexity and shrinkage (both $P<0.05$, one way ANOVA) consistent with the progressive decline in their motor performance. However, in 12 week old SCA1 mice that received doxycycline from 0-6 weeks of age, PN dendrites displayed normal complexity and length compared with controls (both $P>0.05$, one way ANOVA).

These results indicate that developing PNs are more sensitive than mature PNs to ataxin-1 82Q expansion and that this leads to increased severity and progression of SCA1. Our findings support the need for early identification of the SCA1 genotype of affected human families in order to more effectively slow the disease.



Decreased complexity of proximal dendrites of cerebellar Purkinje neurons in a mouse model of SCA1. Red is high complexity, blue is low complexity

Poster Ref: P1-B-023

Theme: B: Molecular, Cellular and Synaptic Mechanisms

The use of induced pluripotent stem cell technology to understand photoreceptor cytoskeletal dynamics in retinitis pigmentosa.

Roly Megaw[1], Carla Mellough[2], Bal Dhillon[1], Alan Wright[1], Linda Lako[2] and Charles ffrench-Constant[1]

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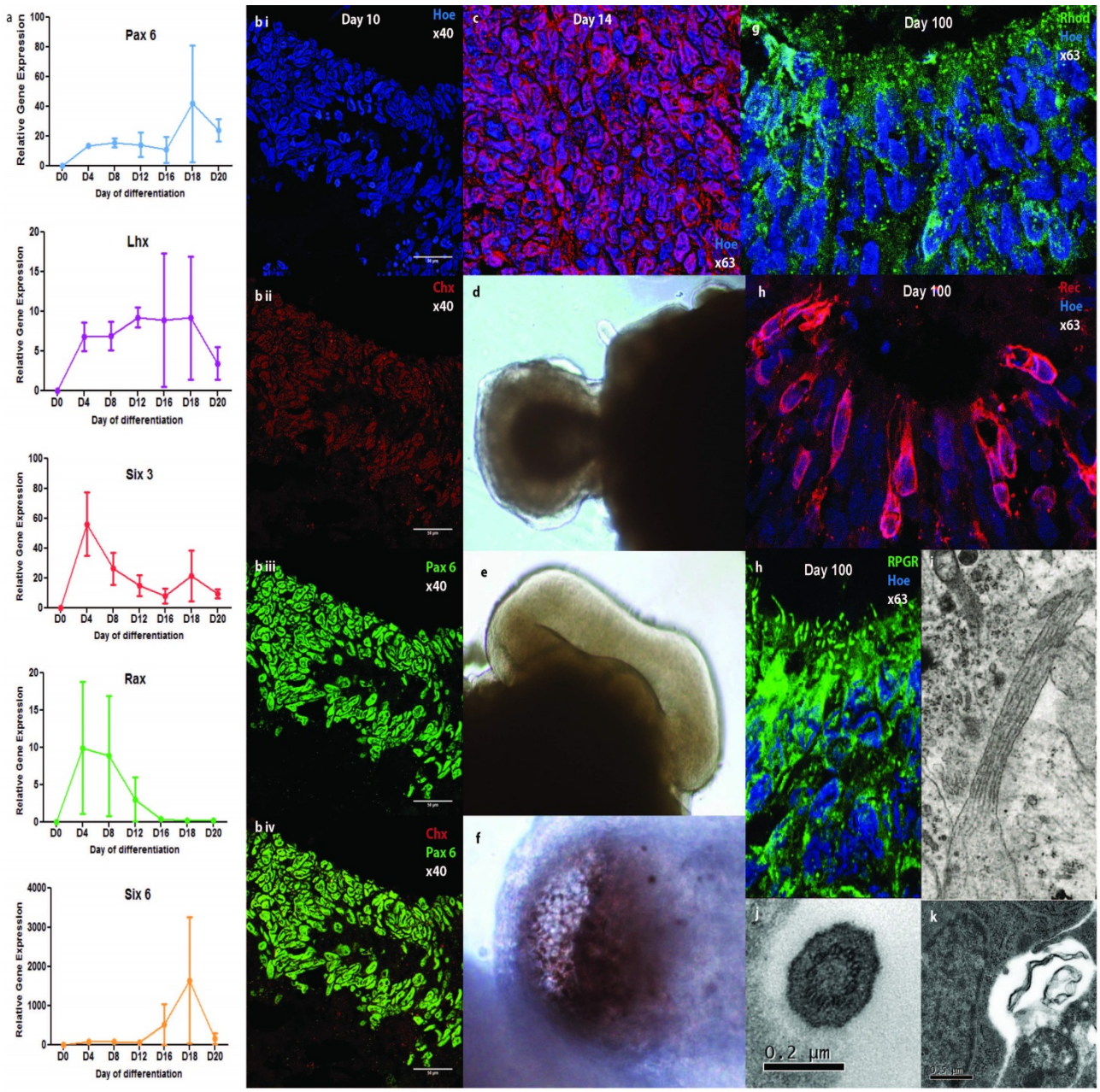
Retinitis pigmentosa affects 1 in 3000 people, causing blindness. It has no treatment. Mutations in the retinitis pigmentosa GTPase regulator (RPGR) gene cause 20% of all cases. Recent work suggests that RPGR, localised to the photoreceptor connecting cilium, regulates rhodopsin transport to the outer segment through its effect on actin turnover. We set out to establish a novel human cell-based model for RPGR disease to test the hypothesis that RPGR mutations lead to retinal degeneration due to a dysregulation of the actin cytoskeleton.

Patients with RPGR mutations and unaffected relatives were recruited and skin biopsy samples taken. Fibroblast lines were reprogrammed to generate induced pluripotent stem cell (iPSC) lines. A three-dimensional organogenesis protocol was optimised whereby embryoid bodies (EBs) were formed and patterned towards an eye field fate in a 100-day retinal differentiation protocol, allowing three-dimensional optic cups to form (see Fig 1). RGPR-mutated cultures were compared with healthy controls.

Mutant and wild-type iPSC lines were generated and characterised. Differentiation of both resulted in optic cup generation in a self-organising manner after 100 days in culture. These cultures contained mature photoreceptors, as evidenced by morphology and both RNA and protein expression. Photoreceptor cultures from RGPR-mutated iPS cells had increased actin polymerisation compared with controls (confocal pixel intensity counts : 59.02 (SD 16.24) vs 23.70 (SD 8.128) p=0•0081). This finding was confirmed by assessment of F-actin with western blot. Pathways regulating actin turnover were explored; western blot analysis showed a reduction in both Src and ERK phosphorylation in RGPR-mutated photoreceptor cultures. An unbiased protein array confirmed this reduction in ERK and Src activation. Several other pathways were also shown to be dysregulated in the RGPR-mutated photoreceptor cultures.

This study supports the hypothesis that RPGR mutations lead to actin dysregulation. We have identified several pathways which are interupted in RPGR-mutant photoreceptor cultures and could be contributing to disease. This study is the first use (to our knowledge) of human iPSCs with retinitis pigmentosa-causing mutations to look at pathophysiology of disease.



Photoreceptor differentiation. Patterned embryoid bodies (EBs) upregulate retinal markers on qPCR (a) and immunostaining (b,c). Optic cups emerge, self organise and mature (d-f). Photoreceptors are organised, expressing mature markers (g,h). RPGR localises to connecting cilia (CC;h). Electron microscopy shows CCs (9+0 microtubule doublets; i,j) depositing membranous material (k).

Poster Ref: P1-B-024

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Nitric oxide modulation of functional synaptic vesicle pool sizes.

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Nitric oxide (NO) signalling is implicated in several neurodegenerative diseases through induction of high concentrations of NO release. However, its exact contribution to degenerative processes remains elusive due to the complexity of downstream nitrergic targets. High levels of NO can induce post-translational modifications which are associated with neuronal degeneration. Elevated NO can react with superoxide anions to form cytotoxic peroxynitrite which in turn can result in the nitration of tyrosine residues leading to largely detrimental changes in protein function. Additionally, toxic NO signalling can alter protein functioning in a process known as S-nitrosylation. To date, little is known as to what extent these NO-mediated post-translational modifications contribute to or exacerbate neuronal dysfunction. Here we use glutamatergic synapses as a model system to identify novel nitrergic signalling pathways to correlate protein modifications with functional changes.

Here we investigate the effects of NO on synaptic function which may involve S-nitrosylation or 3-NT signalling. The Drosophila neuromuscular junction was used as a model to characterise NO-mediated effects employing immunohistochemical and two-electrode-voltage-clamp (TEVC) analyses. Electrophysiological recordings were carried out in HL-3 solution in 1.5mM calcium using sharp electrodes (20-30MΩ). Data denotes mean±SEM (n-number) with *p<0.05 indicating statistical significance using unpaired Student's t-test. Confocal imaging analysis showed elevated levels of S-nitroso-cysteine and 3-Nitrotyrosine at synapses following NO-donor exposure. TEVC data showed little NO (~130nM) effects on miniature excitatory junctional current (mEJCs) amplitudes or decay kinetics but induced a reduction in mEJC frequencies (Ctrl: 1.6±0.1Hz (49) vs NO: 1.0±0.1Hz (24)). Furthermore, evoked EJC amplitudes (Ctrl: 101±5nA (18) vs NO: 48±6nA* (5)) and quantal content (QC; Ctrl: 119±6 (18) vs NO: 75±7* (5)) were strongly reduced following NO exposure for >40min suggestive for a reduction in presynaptic release. Cumulative postsynaptic current analysis (500ms 50Hz train) further showed a reduced number of release-ready vesicles following NO exposure (Ctrl: 382±45 (7) vs NO: 154±44* (5)) which was also confirmed by estimating the number of release sites using fluctuation analysis. The presence of ODQ, a soluble guanylyl cyclase (sGC) inhibitor (10-50μM), did not alter the responses to NO.

Together, our data suggest that NO can induce 3-NT or S-nitrosylation of proteins involved in synaptic signalling possibly leading to protein modifications as detected by changes in synaptic physiology. The physiological data suggest presynaptic actions of NO in a sGC-independent manner. This data extends our understanding of NO signalling, potentially leading to the identification of putative targets for therapeutic intervention(s) in disease.

Poster Ref: P1-B-025

Theme: B: Molecular, Cellular and Synaptic Mechanisms

The function of distinct MAOA proteins in mitochondrial function.

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Monoamine oxidase A (MAOA) is in part responsible for the active concentration of monoamines in the brain. Research has tended to focus in the transcriptional regulation of this gene and in particular a polymorphic variant termed the uVNTR. However there are several isoforms of MAOA that are possible and they lead to distinct proteins. These proteins in all probably are regulated in a tissue specific and stimulus inducible manner and potentially alter MAOA activity in the cell.

An extensive bioinformatics analysis of the MAOA gene from various accredited web browser such as UCSC, AceView, UniProt and Ensemble report several isoforms of the MAOA mRNA which would encode at least two different MAOA proteins.

In vitro analysis on the neuroblastoma cell line SH-SY5Y validated some but not all of the MAOA mRNA isoforms. In addition to the canonical and most abundant isoform, there are

1) a splicing variant with an alternative Exon which contains a TGA stop codon in the reading frame which would result in truncated protein. It also has the potential to then use a novel translational start site in a distinct exon.
2) a 2nd isoform which lacks Exon IV.

The proteins encoded by these mRNA isoforms are likely to result in distinct functions that could also affect our mental health analogous to different concentrations of the 'WT' isoform. We are currently addressing MAOA isoform function using the Seahorse strategy to address mitochondrial function.

Poster Ref: P1-B-026

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Measurement of acetylcholine release in the hippocampus during behaviour using amperometric sensors.

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Acetylcholine plays a critical role in hippocampal function by controlling cellular, synaptic and network properties. Insight into the dynamics of acetylcholine release in the rodent brain during different behavioural states has so far largely been provided by microdialysis studies, which have a temporal resolution limited to the order of minutes and a spatial resolution >100µm. Newly developed biosensors that use enzymatic redox reactions to detect the release of neurotransmitters have made possible the measurement of neurotransmitter release at sub-second timescales and at spatial resolutions <100µm. For the measurement of acetylcholine, the enzyme choline oxidase is embedded into a polymer matrix coated on a metal electrode that detects the current produced by the oxidation of choline. Thus, these sensors detect choline production resulting from acetylcholine breakdown by endogenous acetylcholinesterase.

Fast choline transients that increase and decrease over a period of a few seconds have been reported in the prefrontal cortex of rats performing an attentional task. However, the kinetics of acetylcholine release in the hippocampus of freely moving animals at high temporal resolution is largely unknown. Here we report changes in acetylcholine release in the dorsal hippocampus of adult mice during different behavioural states. We first correlate these changes with different phases of sleep including REM, and non-REM as well as phases of wakefulness. Finally, we correlate changes in acetylcholine release during performance of mice on a hippocampal-dependent behavioural task. We find that acetylcholine release is dynamically regulated during sleep and correlates with specific behavioural states.

Poster Ref: P1-B-027

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Probing the mechanisms behind pyramidal cell firing in hippocampal sharp waves.

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Sharp wave ripples (SWRs) are a transient hippocampal oscillation, during which sequences of place cell activity reactivate in a temporally compressed manner. This has been hypothesised to facilitate spatial memory consolidation during off-line behavioural states. However, precisely what governs which spatial trajectories are replayed and therefore the cellular mechanisms that select which hippocampal pyramidal cells are active during specific SWRs remains to be conclusively determined. Here we address this question by combining *in vitro*, mouse hippocampal recordings with analysis of a computational model of the hippocampal CA3-CA1 network (Taxidis *et al.*, 2012).

We confirm that excitation and inhibition are critical for the emergence of sharp waves *in vitro* and that a single pyramidal cell receives a combination of both during sharp waves. The balance of synaptic currents in CA3 favours inhibition whereas in CA1 there are a subset of cells with predominantly excitatory inputs. The model predicts that the strength of excitatory connectivity and the general excitability of pyramidal cells are important for governing their participation in SWRs, while inhibition surprisingly does not appear to play such an important role.

References.

Taxidis J, Coombes S, Mason R & Owen MR. (2012). Modeling sharp wave-ripple complexes through a CA3-CA1 network model with chemical synapses. Hippocampus 22, 995-1017.

Poster Ref: P1-B-028

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Distinct regions within the GluN2C subunit regulate the surface delivery of NMDA receptors.

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N-methyl-D-aspartate (NMDA) receptors are a class of ionotropic glutamate receptors, involved in excitatory synaptic transmission, synaptic plasticity and excitotoxicity. They form heterotetrameric complexes composed of GluN1, GluN2A-D and/or GluN3A-B subunits that are activated by glutamate and glycine. Previous reports showed that different subunits of NMDA receptors, especially the GluN2 subunits, confer different functional and pharmacological properties on the receptor complexes. However, the subunit-dependent differences in the regulation of intracellular processing and transport of NMDA receptor subtypes has not been clearly elucidated. The aim of this work was to clarify the mechanisms of regulation of the NMDA receptor transport. In our experiments we performed immunocytochemistry and electrophysiology of receptors on heterologous COS-7 cells and cultured cerebellar granule cells (CGC), both expressing recombinant NMDA receptors. The results of this work show that the transport of NMDA receptors is regulated by presence of GluN2A and GluN2B subunits. Our results further showed that transport of the GluN1/GluN2C receptors is regulated by three specific areas of the GluN2C subunit: i) the A2 segment within the amino-terminal domain, ii.) the M3 domain, and iii.) the proximal part of the C-terminus containing the sequence of five amino acids, SLPSP. Our results help clarify the mechanisms regulating the function of NMDA receptors in the mammalian central nervous system and thus contribute to our understanding of the mechanisms involved in various neurological and psychiatric disorders associated with abnormal regulation of NMDA receptors.

This work was supported by the Grant Agency of the Czech Republic (14-09220P, to Martina Kaniakova; 14-02219S, to Martin Horak; and P303/12/1464, to Ladislav Vyklicky), the Grant Agency of Charles University (1520-243-253483, to Katarina Lichnerova), a Marie Curie International Reintegration Grant (PIRG-GA-2010-276827; to Martin Horak), a Research Project of the AS CR (RVO:67985823) and BIOCEV – Biotechnology and Biomedicine Centre of Academy of Sciences and Charles University in Vestec, project supported from European Regional Development Fund.

Poster Ref: P1-B-029

Theme: B: Molecular, Cellular and Synaptic Mechanisms

TLR3 activation results in the inhibition of synaptic activity in primary hippocampal cultures.

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Toll like receptors (TLRs) belong to a family of pattern recognition receptors that recognise broadly shared molecules found on pathogens referred to as pathogen associated molecular patterns (PAMPs). TLRs are well known for their involvement in innate immunity however despite their presence in the CNS, our knowledge of their function in the CNS is limited. Therefore in the present study, we investigated the cellular localisation of TLR3 and the consequence of its activation on synaptic activity in primary hippocampal cultures. Immunocytochemical studies showed TLR3 to be present in neurons, astrocytes and oligodendrocytes in primary hippocampal cultures. Synaptic activity was examined using whole cell patch clamp in the current clamp and voltage clamp mode. Synaptically driven spontaneous action potential (AP) firing was significantly reduced by the acute application (5min) of the TLR3 specific activator, poly I:C (25µg/ml: 84.9 ± 2.7% of control; 200µg/ml: 68.3 ± 8.1% of control, n=6 for all, $P<0.05$). Furthermore chronic poly I:C application (1 hr) resulted in a dramatic reduction in AP firing (1µg/ml: 67.3 ± 3.2 AP/min, n=6, $P<0.01$; 25µg/ml: 1.6 ± 0.9 AP/min, n=8, $P<0.001$) in comparison to control (163.4 ± 15.9 AP/min, n=17). In agreement with this, poly A:U, another TLR3 activator, resulted in a significant reduction in AP firing when applied chronically (25µg/ml: 50.2 ± 10 AP/min, n=6, $P<0.01$). In addition, chronic application of poly I:C resulted in a significant reduction in sodium (Imax control: 1003.8 ± 67.8, n= 22; Imax 25µg poly I:C: -111.3 ± 74.6 pA, n=5, $P<0.001$). These data imply that TLR3 activation modulates hippocampal synaptic activity. Investigations regarding the mechanisms underlying these effects are on-going and will give further insight into the role TLR3 plays in modulating synaptic activity and how this contributes to virally-mediated behavioural changes.

Poster Ref: P1-B-030

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Development of an antisense oligonucleotide-based method to manipulate RNA editing of AMPAR subunits.

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Background: AMPA receptors (AMPARs) are a subset of ionotropic glutamate receptor composed of one or more of four subunits (GluA1-4). AMPARs play a central role in normal and abnormal synaptic function within the nervous system and are permeable to calcium unless the GluA2 subunit is present. GluA2 subunits undergo RNA editing at a specific adenosine, resulting in a change in amino acid residue from glutamine to arginine, critical for regulating calcium permeability. RNA editing is performed by a family of enzymes called Adenosine Deaminases Acting on RNAs (ADARs) and is highly dependent on the double-stranded structure of the RNA transcript. ADAR2 exists as multiple alternatively-spliced variants within mammalian cells and some have been shown to reduce the efficiency of ADAR2 deamination. RNA editing in AMPAR subunits is inefficient in patients with Amyotrophic Lateral Sclerosis (1) and manipulating this process could be a potential therapeutic strategy against AMPAR-triggered neuronal cell death.

Objectives: To manipulate RNA editing of AMPAR subunits using antisense oligonucleotides (ASO), either by disrupting the GluA2 double-stranded RNA structure or by altering the alternative splicing of ADAR2.

Methods: The effects of specific ASOs on RNA editing were assessed by cotransfection of ASOs and a plasmid containing a section of the GluA2 genomic DNA into HeLa cells. Editing was quantified by a RT-PCR based assay on RNA extracts followed by densiometric analysis of BbvI digestion products.

Results: 10 μM of two 25mer ASOs targeting the GluA2 RNA transcript reduced editing (92.3 ± 1.58% and 70.7 ± 0.44% compared to controls, n=3). Furthermore, ASOs were found to efficiently inhibit the expression of a less efficient form of ADAR2 (ADAR2-AluJ) (99.37 ± 0.41% AluJ exclusion compared to natural AluJ exclusion of 40.77 ± 0.62%). Consequently, we observed an increase in RNA editing of 24 ± 1.44% from baseline (n=6, $p<0.05$).

Conclusion: This data shows that ASOs can be used to manipulate RNA editing and we are now examining the effects of our ASOs in neuronal-like cell lines (differentiated NSC34s and SHSY5Ys) known to endogenously express the GluA2 subunit.

Acknowledgements: This work was supported by the MNDA.

Reference: Kawahara, Y. *et al.* Nature, (2004) 427: 801.

Poster Ref: P1-B-031

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Unbalanced peptidergic inhibition in superficial neocortex underlies spike and wave seizure activity.

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Spike and wave discharges (SpW) are a feature of many types of epilepsy. They are linked to pathology of the thalamocortical axis and a thalamic mechanism has been elegantly described. Here we present evidence, using *in vitro* and *in vivo* electrophysiology, combined with computational modelling, for a separate generator of SpW in local circuits of associational areas of neocortex manifest from a background, sleep-associated delta rhythm. Furthermore, using *in vitro* electrophysiology combined with immunohistochemical techniques, we propose a mechanism for this cortical generation of SpW. All animal work conformed to the Scientific Animal Procedures Act, (1986).

Loss of tonic neuromodulatory excitation, mediated by nicotinic acetylcholine or serotonin (5HT3A) receptors, of 5HT3-immunopositive interneurons caused an increase in amplitude and slowing of the delta rhythm until each period became the 'wave' component of the spike and wave discharge. As with the normal delta rhythm the 'wave' of a spike and wave discharge originated in cortical layer 5. In contrast, the 'spike' component of the spike and wave discharge originated from a relative failure of fast inhibition in layers 2/3 - switching pyramidal cell action potential outputs from single, sparse spiking during delta rhythms to brief, intense burst spiking phase locked to the 'spike'.

The mechanisms underlying this loss of superficial layer fast inhibition, and a concomitant increase in slow inhibition, appear to be precipitated by a loss of NeuropeptideY (NPY)-mediated local circuit inhibition and a subsequent increase in Vasoactive Intestinal Peptide (VIP)-mediated disinhibition. Blockade of NPY Y1 receptors is sufficient to generate spike and wave discharges whereas blockade of VIP receptors almost completely abolished this form of epileptiform activity.

These data suggest that aberrant, activity-dependent neuropeptide co-release can have catastrophic effects on neocortical dynamics.

This work is supported by the Wellcome Trust.

Poster Ref: P1-B-032

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Region-specific differences in cortical delta rhythms.

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University of York

Delta rhythms (0.4 – 4 Hz) are a characteristic feature of slow wave sleep in mammals. While a thalamic or thalamocortical origin has been proposed, the regional neocortical variance in occurrence *in vivo* and the ability to generate delta rhythms in isolated neocortex *in vitro* suggest local circuits in cortex are sufficient – at least in association cortex (1). Here we directly compare the dynamic profile, and laminar-specific neuronal involvement of delta rhythms generated in primary somatosensory (S1) cortex and parietal (par2, association) cortex to better understand how ubiquitous local circuit neocortical delta generation may be.

Thalamocortical slices (450 µm thick) were acutely prepared from adult male rats, maintained *in vitro* and two 4 x 8 electrode arrays placed side-by-side to cover adjacent S1 and par2. Delta rhythms were generated as per ref 1. Both regions generated persistent delta rhythms with power dominant in layer 5. However, significant differences in frequency were seen between S1 and Par2. This was accompanied by poor, unstable phase relationships between the two adjacent areas as revealed by crosscorrellograms between pairs of laminae in the two regions. To investigate further, unit activity was examined in each area. Spikes were subdivided into putative fast –spiking (interneuron) and slow-spiking neuron subtypes on the basis of shape. In both regions fast spikes were concentrated in layers 1-2 and 6 whereas slow spikes were dominant in layer 5. Spike correlation with local field potential delta revealed a robust 30 – 120° difference when comparing S1 with par2. Surgical separation of S1 and par2 accentuated these differences dramatically.

These data suggest that different local circuit delta rhythm generators may exist in cortical areas subserving different functions.

Supported by The Wellcome Trust.

1) Carracedo, Lucy M, *et al.* 2013 The Journal of Neuroscience 33.26: 10750-10761.

Poster Ref: P1-B-033

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Gamma and beta oscillations control stellate neuron output in layer IV of the rat primary visual cortex.

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University of York

The visual cortex is one of the most specialized sensory structures in the brain. Its laminar structure is different from all other brain regions, it possesses a highly developed and neuronally heterogeneous layer IV (the main input layer from visual thalamus). It is the source of a rich array of brain rhythms which have been proposed to underlie a range of cognitive functions from primary sensory processing (low gamma, 30-50 Hz), short term memory (beta, 12-30 Hz) and selective attention (alpha, 9-12 Hz). In this study we examined the consequences of two of these brain rhythms, in the gamma and the beta bands, for stellate cell output.

Coronal sections of the visual cortex containing the V1 and V2 structures were isolated from adult, male wistar rats (~150g) in 450μm thick slices. Extracellular field potential (LFP) recordings were taken from all layers and regions of the primary visual cortex. All animal work conformed to the UK Home office Animals (Scientific Procedures) Act, 1986.

Activation of the primary visual cortex with bath application of 800nM kainate generated both gamma (40.7Hz ± 1.3Hz, 10.1μV ± 3.7μV, n=19) and beta oscillations (27.2Hz ± 0.9Hz, 12.5μV ± 2.6μV, n=31) which were particularly prominent in V1M. There were low power beta oscillations in both the superficial and deep layers of the V1 with the rhythm dominating in the main input layer IV (26Hz ± 2.4Hz, 17.6μV ± 5.8μV). A similar pattern of laminar activity was observed for the gamma rhythm in which low gamma was observed in both superficial and deep layers, with the largest gamma power observed in layer IV (37.1Hz ± 1.2Hz, 17.6μV ± 2.8μV). In the case of both rhythms, trains of inhibitory postsynaptic potentials (IPSPs) dominated in stellate cells phase locked to the LIV field potential rhythm. These IPSPs controlled the probability of action potential timing such that stellate cell output - with rates of 3 – 10 Hz at rest - was also phase locked to the layer IV field.

These data suggest that, unlike in primary auditory cortex1, V1 low gamma rhythms are generated in layer IV rather than supragranular layers and beta rhythms in this area do not require cholinergic neuromodulation for their generation.

Funded by the Wellcome Trust.

1. Ainsworth M *et al.* (2011) J Neurosci 31(47): 17040-51.

Poster Ref: P1-B-034

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Hypothermic preconditioning of human cortical neurons: coupling neuroprotection to ontogenic reversal of tau.

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Hypothermia is potently neuroprotective but the molecular basis of this effect remains obscure, and the practical challenges of cooling have restricted its clinical use. Considerable therapeutic potential may lie in a deeper understanding of the neuronal physiology of cooling. Rodent studies indicate that hypothermia can elicit preconditioning whereby a transient, subtoxic stress confers resistance to an otherwise lethal injury. This cooling-induced tolerance requires de novo protein synthesis – a fundamental arm of the cold-shock response, for which data in human neurons is lacking. Since cooling protects the human neonatal brain, experiments herein address the molecular effects of therapeutic hypothermia using functional, maturationally-comparable cortical neurons differentiated from human pluripotent stem cells (hCNs). Several core hypothermic phenomena are explored in hCNs with particular scrutiny of neuronal tau, since this protein is modified extensively in brains that are resistant to injury. Mild-to-moderate hypothermia produces an archetypal cold-shock response in hCNs and protects them from oxidative and excitotoxic stress. Principal features of human cortical tau development are recapitulated during hCN differentiation, and subsequently reversed by cooling, returning tau transcriptionally and post-translationally to a fetal-like state. These findings provide the first evidence of cold-stress-mediated ontogenic reversal in human neurons. Furthermore, neuroprotective hypothermia induces mild endoplasmic reticulum (ER) stress in hCNs, with subsequent activation of the unfolded protein response (UPR). Reciprocal modulation of both tau phosphorylation and the ER-UPR cascade suggests that cold-induced hyperphosphorylation of tau and ER-hormesis represent significant components of hypothermic neuroprotection. Cooling thus modifies proteostatic pathways in a manner that favours cytoprotective outputs of the UPR. To date, hypothermia has protected hCNs against oxidative, excitotoxic and ER stress, all of which feature in traumatic as well as degenerative processes. This ‘cross-tolerance’ effect places incremental value on the molecular neurobiology of cooling, with the potential to extract multiple therapeutic targets for an unmet need.

Poster Ref: P1-B-035

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Inhibitory short-term depression enables excitatory gain modulation in cerebellar nucleus neurons.

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Neuronal responses result from the combination of multiple input sources that can either drive or modulate the output of the neuron. The integration of signals is often additive, with a modulatory input resulting in a shift of the neuron's input-output (I-O) function along the input rate axis. However, multiplicative operations are also widespread, and they play an important role in neuronal computations.

Various factors and neuronal processes can affect how neurons combine information. One of these processes is short-term depression (STD), the depression of a neuron's response to synaptic input. In the cerebellar cortex, STD at excitatory synapses between mossy fibres (MFs) and granule cells has been found to control neuronal gain [1]. However, STD can also be present at inhibitory synapses. For example, the output of cerebellar cortex arises from Purkinje cells (PCs), which drive cerebellar nucleus (CN) neurons with inhibitory input that exhibits STD. Here we study how STD at the inhibitory synapse from PCs to CN neurons can affect the output of the CN neurons.

To investigate the effect of STD at this inhibitory synapse, we use a biologically realistic model of a CN neuron [2], providing the neuron with both excitatory and inhibitory input in the presence and absence of inhibitory STD. We identify the I-O function in the absence of STD, and show that excitatory input shifts the I-O function along the input rate axis, performing an additive operation. We then introduce STD at the inhibitory synapse, which results in a gain change in the I-O function of the CN neuron. Most importantly, we demonstrate that the introduction of STD at the inhibitory synapse leads to a change of the effect of excitatory input, adding a gain change to the previously shown shift along the input rate axis. This suggests that STD in the inhibitory input from PCs to CN neurons can introduce a multiplicative component to the otherwise additive operation performed by the modulatory input from MFs.

[1] Rothman, J. S., Cathala, L., Steuber, V., and Silver, R. A. Nature, 457(7232):1015–1018 (2009).
[2] Steuber, V., Schultheiss, N. W., Silver, R. A., De Schutter, E., and Jaeger, D. Journal of Computational Neuroscience, 30(3):633–58 (2011).

Poster Ref: P1-B-037

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Coordinated activation of distinct Ca^{2+} sources and mGluRs encode hebbian plasticity at mature hippocampal Schaffer collateral synapses.

Cezar M. Tigaret, Valeria Olivo, Josef H. L. P. Sadowski, Michael C. Ashby and Jack R. Mellor

University of Bristol

Induction of spike timing-dependent synaptic plasticity at mature Schaffer collateral synapses onto CA1 hippocampal pyramidal neurons requires specific timing between synaptic input and postsynaptic spikes to activate postsynaptic NMDA receptors (NMDARs). The ensuing Ca^{2+} transients in dendritic spines (EPSCaTs) are proposed to determine the magnitude and direction of plasticity. We evaluated spike timing-dependent plasticity at Schaffer collateral to CA1 pyramidal neuron synapses in acute hippocampal slices from adult rats, by pairing pre-synaptic stimuli in stratum radiatum with somatically-evoked postsynaptic spikes. Using two-photon Ca^{2+} fluorescence imaging we show that the amplitude of EPSCaTs induced by paired activity at mature hippocampal Schaffer collateral synapses does not match the observed plasticity induction rule. Recordings were performed in whole-cell current clamp, at 36˚C, under GABAA receptor inhibition (50 μM picrotoxin). In contrast, induction of NMDA receptor-dependent LTP required by time-correlated pre- and post-synaptic spikes requires the sequential activation of NMDARs followed by voltage-sensitive Ca^{2+} channels within dendritic spines. Furthermore LTP requires mGlu1-dependent inhibition of SK channels to promote NMDAR activation. We conclude that induction of LTP by time-correlated pre- and post-synaptic activity requires the activation of distinct sources of Ca^{2+} and the recruitment of an mGluR1-dependent inhibition of a negative feedback loop that targets the activation of NMDARs.

Poster Ref: P1-B-038

Theme: B: Molecular, Cellular and Synaptic Mechanisms

The role of MSK1 in experience dependent remodelling of hippocampal synaptic plasticity.

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Sensory, motor, and cognitive stimuli, resulting from interactions with the environment, play a key role in modifying the neuronal connectivity required for normal brain function. An experimental animal model for this phenomenon is provided by environmental enrichment (EE) in rodents. EE causes profound changes in neuronal structure and function throughout the brain, including the hippocampus. Brain-derived neurotrophic factor (BDNF) has repeatedly been implicated as responsible for initiating the molecular events that convert sensory experience into enduring changes at the cellular and behavioural level.

Mitogen- and stress-activated protein kinase 1 (MSK1) is activated following stimulation of TrkB receptors by BDNF. MSK1 subsequently regulates gene transcription *via* phosphorylation of its downstream targets CREB and histone H3. We have previously demonstrated that mice carrying an inactivating kinase-dead (KD) knock-in point mutation of the MSK1 gene failed to show synaptic adaptation in response to environmental enrichment (Correa *et al.* 2012). This suggests that MSK1 is a key regulator of experience-dependent synaptic adaptation, an action that likely revolves around its ability to directly influence transcription.

In the current study we explored whether EE improved hippocampus-dependent basal synaptic transmission and long-term potentiation (LTP) in an MSK1-dependent manner. To this end, we reared wild-type (WT) and MSK1 kinase dead (MSK1 KD) mice in standard conditions or in EE from birth to 2.5-4 months of age.

MSK1 KD mice displayed smaller fEPSPs compared to WT mice but had similar presynaptic fiber volley amplitudes and paired-pulse facilitation. These parameters were not influenced by housing status. In preliminary experiments we observed a positive effect of EE in WT, but not MSK1 KD mice.

These data and a parallel study of hippocampus-dependent spatial reference and working memory (More *et al.*; this meeting) are investigating the possibility that MSK1 is an important transducer of positive environmental stimulation into long-lasting structural and functional neuronal adaptations that underpin the enhanced cognition associated with enrichment.

Correa, S.A., *et al.*, J Neurosci, 2012. 32 13039-51.

Poster Ref: P1-B-039

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Claustrum as a high frequency gamma coordinator.

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The claustrum is a subcortical thin layer of gray matter in the basolateral telencephalon of the mammalian brain. Consistent with the latin derivation of its name 'hidden place' it lies hidden, separated from the insular cortex by the extreme capsule and, medially, from the lenticular nucleus by the external capsule. Detailed anatomical characterisation of its interconnected glutamatergic projection neurons (pyramidal cells) and GABAergic interneurons has only been undertaken from the early 1980s. The function of claustrum remains enigmatic too. It is known to have reciprocal anatomical projections to different regions of the cortex (frontal, premotor, ventral anterior cingulate, ventral temporal, visual, motor, somatosensory, olfactory cortices, entorhinal cortex) as well as to subcortical structures (putamen, globus pallidus, lateral amygdala). Based upon these connections it has been suggested that the claustrum might play a key role in information processing and integrating multisensory information through higher-order cross-frequency interactions (Smythies *et al.*, 2012).

Using 450 µm thick coronal slices from adult male rats, gamma rhythms were induced in claustrum by bath application of 200-800nM Kainate and 20 µM carbachol. Stable, persistent gamma rhythms were generated in the claustral cell syncytium over a range of frequencies encompassing both low and high gamma bands (38-86Hz). A robust, stable frequency gradient was seen in which lower frequencies were present in the ventral part of the claustrum and higher frequencies in the dorsal part.

Continuous frequency gradients such as that seen in claustrum are rare in cortex. Thus we conclude that the claustrum uses such gradients to combine, *via* local circuit interactions, inputs from multiple cortical sources at different gamma frequencies.

Supported by the Wellcome Trust.

Front Integr Neurosci. 2012 Aug 2;6:53. doi: 10.3389/fnint.2012.00053. eCollection 2012. Hypotheses relating to the function of the claustrum. Smythies J1, Edelstein L, Ramachandran V.

Poster Ref: P1-B-040

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Modulation of hippocampal gamma oscillations by acetylcholine: an *in vitro* optogenetic and computational investigation.

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A neuronal oscillation involves the rhythmic, synchronised firing of a population of cells. Gamma frequency oscillations (30-100Hz) are associated with a variety of cognitive functions including attention, sensory processing and learning and memory. Acetylcholine (ACh) release is associated with an increase in the power of hippocampal gamma oscillations and selective knockout of ACh receptor (AChR) subtypes has provided evidence to support this scenario. To understand the detailed mechanisms underlying the modulation of gamma oscillations by ACh we have utilised both *in vitro* and computational models.

A computational model of the hippocampal CA3 network was developed. Comprising of 100 biophysical Hodgkin-Huxley type pyramidal cells and interneurons, the model produced oscillatory activity within the gamma frequency range.

In parallel, we developed an optogenetic system for eliciting gamma frequency oscillations in hippocampal slices. Male mice received stereotaxic injection into the CA3 region of the hippocampus of a viral vector (AAV5) containing channelrhodopsin (hChR2(H134R)) under the control of the CaMKIIα promoter. 470nm light stimulation (5-50ms) to the ChR expressing CA3 pyramidal cells evoked action potentials and robust synaptic responses. A 1s step stimulation elicited low power and low frequency gamma oscillations which attenuated over time. A 5Hz sine wave of optical stimulation evoked robust theta-nested gamma oscillations with properties similar to those seen *in vivo*.

In the computational model, consistent with the *in vitro* model, stimulation of the pyramidal cells with a 1s step or 5Hz sine wave input to pyramidal cells induced gamma oscillations. In further model simulations, modification of specific currents predicted likely receptor subtypes responsible for the modulation of gamma oscillations.

In both *in vitro* and computational systems, activation of AChRs modulated the power of theta-nested gamma frequency oscillations confirming previous observations. In particular, the activation of M1 muscarinic receptors replicated most of the observations implicating M1 receptors as a major regulator of gamma frequency oscillations in the hippocampus.

Poster Ref: P1-B-041

Theme: A: Development

Heterogeneous AMPA receptor trafficking in metabotropic glutamate receptor induced long term depression.

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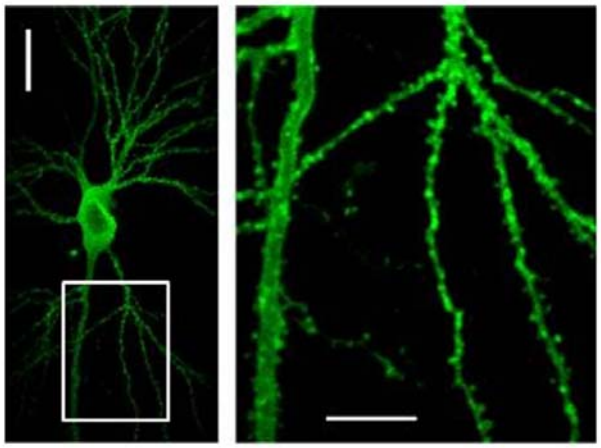
Information is thought to be encoded in the mammalian brain by changes in synaptic strength. One of the major ways that synaptic strength is altered is by AMPA receptor trafficking at the post-synapse, however whether this occurs in a uniform way across all synapses is unknown. In this study we used the AMPA receptor subunit GluA2 tagged with the pH sensitive variant of GFP, super ecliptic pHluorin (SEP), to image surface expressed AMPA receptors. We studied this construct in organotypic hippocampal slices using two photon microscopy during long term depression induced by activation of metabotropic glutamate receptors (mGluR-LTD). We found that 100 μM DHPG applied in the presence of an NMDA receptor antagonist resulted in a reduction in synaptic transmission to 47 + 10 % of baseline, 30 min after DHPG wash out. This form of LTD in our conditions was not accompanied by a change in paired pulse facilitation (99 + 11 %, 30 min after DHPG washout) indicating that it is expressed by a post-synaptic mechanism. Also this LTD was induced by mGluR1 receptors as it was blocked by the specific antagonist LY367385 (100 μM) but not the mGluR5 antagonist MPEP (10 μM), values were 87 + 9 % and 45 + 8 %, respectively. Biolistic transfection of SEP-GluA2 did not affect basal synaptic transmission as AMPA/NMDA ratios in transfected and un-transfected neighbouring neurons were similar (1.1 + 0.1 and 1.2 + 0.2, respectively). Also, the magnitude of mGluR-LTD was similar (62 + 5 % and 57 + 14 %, respectively), indicating that this tool is suitable for studying mGluR-LTD. Imaging of SEP-GluA2 revealed that in control conditions there was significant variability in AMPA receptor surface expression, as a cumulative probability plot of changes in spine fluorescence showed both decreases and increases in fluorescence. In the same conditions to those used for electrophysiology experiments SEP-GluA2 showed enhanced variability when treated with DHPG. A cumulative probability plot of changes in spine fluorescence was significantly different to the control data set ($p<0.05$, KS test) and indicated that the predominant effect was for spines to show greater decreases in fluorescence, however some spines also showed increases. Thus, in our conditions DHPG induced AMPA receptor trafficking differently, depending on the synapse.



Pyramidal neuron expressing SEP-GluA2 in area CA1 of an organotypic hippocampal slice. Scale 20 μm, inset 10 μm.

Poster Ref: P1-B-042

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Regulation of anxiety-related behaviours by Otx2 transcription factor.

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In post-natal development, neural circuitry can be modified in response to experience during critical periods (CP). This cortical plasticity remodelling is driven by the maturation of parvalbumin-expressing inhibitory neurons (PV-cells) and CP time-points differ between each sensory modalities. In the primary visual cortex, CP for binocular vision is triggered by the internalization by PV-cells of Otx2 homeoprotein en route from the choroid plexus. This transfer is necessary and sufficient to open and close plasticity. Moreover, in the adult, blocking this transfer reopens a window of plasticity in the visual cortex. Most importantly, Otx2 import by PV-cells takes place throughout the cerebral cortex, strongly suggesting that Otx2 may regulate plasticity outside of the visual system.

The expression of Otx2 by ventral tegmental area (VTA) dopaminergic neurons and its presence (following transfer) in amygdala PV-cells has fostered the idea that it might also regulate the maturation of complex "social" behaviours. We investigated the anxiety-related behaviour of mice heterozygous for Otx2 (Otx2-het). Among many traits that were analysed, we find that Otx2-het mice are less anxious than their wild type littermates in the elevated-plus maze and light-dark box paradigms. Preliminary results show that the reduced Otx2 levels in the VTA of these mice does not affect the levels of cortical dopamine, suggesting that the hypo-anxiety behaviour is regulated by cortical non-cell autonomous Otx2.

To have a better insight into the non-cell autonomous mechanisms, we have developed transgenic mice secreting a single-chain antibody (scFv) that neutralizes Otx2 in the extracellular space and blocks its signalling activities. In the developing cortex of PV::Cre;scFv mice, Otx2 neutralization delays the expression of plasticity genes, including Arc and fos. Conversely, the induced secretion of the anti-otx2 scFv by the adult choroid plexus leads to a reactivation of plasticity genes in the visual cortex. We are presently applying this novel technology to verify Otx2 role in anxiety behaviour.

Poster Ref: P1-B-043

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Leptin differentially regulates hippocampal synaptic plasticity in an age-dependent manner at temporoammonic-CA1 synapses.

Gemma McGregor and Jenni Harvey

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It is evident that the adipocyte-derived hormone leptin is essential in satiety as a means to maintain energy expenditure. However previous studies have indicated a role for leptin in its ability to regulate excitatory synaptic transmission within the hippocampus and thereby in learning and memory. Investigations have indicated that leptin can modulate synaptic plasticity in an age-dependent manner at Schaffer collateral (SC)-CA1 synapses (Moult and Harvey, 2011). However the effects of leptin on the anatomically distinct temporoammonic (TA) input to CA1 neurons is not known. Here, we have used extracellular recordings to examine the effects of leptin on excitatory synaptic transmission at (TA)-CA1 synapses. Transverse hippocampal slices (350μM) were prepared from 11-18 day or 3-4 month old rats and perfused with oxygenated aCSF. In juvenile slices (P11-18) leptin (100nM; 15mins) resulted in a persistent increase in synaptic transmission (122 ± 4.1% of baseline; n=7; $p<0.05$) *via* activation of GluN2B-containing NMDA receptors and the PI 3-K pathway This leptin effect partially occludes classical HFS (100Hz, 1sec)-induced LTP at TA-CA1 synapses (124 ± 3.0% of baseline; n=7; $p<0.05$) which also involved GluN2B-containing NMDA receptors but required activation of the opposing ERK pathway. Conversely, leptin (25nM; 15mins) evokes a persistent decrease in synaptic transmission at TA-CA1 synapses in adult (3-4 month) slices (77 ± 5.0% of baseline; n=4; $p<0.05$). This effect is mediated by GluN2A-containing NMDA receptors and the ERK signalling cascade. Interestingly, classical LFS (1Hz, 900 shocks) also induced LTD at adult TA-CA1 synapses (63 ± 8.0% of baseline; n=5; $p<0.05$). LFS-induced LTD partially occludes leptin-induced LTD however LFS-induced LTD occurs independently of NMDA receptor activation. Understanding how leptin can modulate hippocampal excitatory synaptic function during development and ageing is important as the TA pathway plays a key role in spatial novelty detection and intermediate-term working memory as well as being linked to neurodegeneration in Alzheimer's disease (Vago & Kesner, 2008; Buxbaum *et al.* 1998; Yassa *et al.* 2010). Therefore these findings have important implications for leptin's role in health and disease.

Theme C: Sensory and Motor Systems

Posters P1-C-001 to P1-C-031

Poster Ref: P1-C-001

Theme: C: Sensory and Motor Systems

Environmental enrichment and striatal perineuronal net digestion exert opposing effects upon the performance of mice in a cognitive behavioural task.

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Introduction: Environmental enrichment (EE) provides extra sensory, motor and social stimuli. Perineuronal nets (PNNs) are important for the maintenance of circuit integrity. Both EE and PNN digestion increase plasticity within neural circuits. We investigated the effect of EE and striatal PNN dissolution upon animal performance within a Puzzle-Box task assessing goal-orientated learning and problem-solving, and a Rotarod task testing sensorimotor coordination.

Methods: Animals were raised in enriched and standard housing from birth. PNNs were dissolved *via* bilateral striatal infusion of Chondroitinase ABC (ChABC). Six groups of animals were assessed: standard and EE no surgery (S, n=18; E, n=21); standard and EE vehicle infusion (SV, n=7; EV, n=13); and standard and EE ChABC infusion (SC, n=8; EC, n=13). Performance of animals was assessed by time taken to enter the goal-zone of the Puzzle-Box, and time spent upon the Rotarod. Video recordings were made and behavioural patterns of animals within the Puzzle-Box analysed. Repeated measures ANOVA and univariate ANOVA with housing condition and surgical status as between-subjects factors were used to analyse data.

Results: E animals took significantly less time to solve the Puzzle-Box task than S animals ($P=0.008$), spent less time next to the wall ($P<0.001$), more time approaching obstruction puzzles ($P<0.001$) and had lower levels of locomotor activity ($P<0.001$). ChABC animals took significantly longer to solve the Puzzle-Box task than non-surgery animals ($P<0.001$) and displayed differing movement patterns. EC animals showed significantly shorter performance latencies than SC animals ($P<0.001$). E and EV animals showed improved task acquisition upon the Rotarod apparatus compared to S and SV animals.

Conclusions: EE improved motor task acquisition in a test of sensorimotor coordination, and problem-solving in a goal-orientated learning task in which it also prevented the full behavioural effects of striatal ChABC infusion. Changes in movement patterns and locomotion suggest that EE increases motivation to escape from the Puzzle-Box apparatus. EE and ChABC induced opposing behavioural changes, suggesting that the plasticity effects of enrichment and PNN digestion do not share common mechanisms.

Poster Ref: P1-C-002

Theme: C: Sensory and Motor Systems

Effect of ethnic group and age similarity on action understanding and imitation in children with ASD.

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'Mirror Neuron Theory' is a brain process model which is based on a direct-matching model, that encodes the motor features, mental states, and the goal of observed actions onto the observers own motor system. Mirror neuron abnormalities and Autism Spectrum Disorder ASD have been empirically associated as they are alleged to represent the neural basis of deficits in social competence and imitative learning in ASD.

Neurophysiological evidences nonetheless appear to validate the enhanced activity of mirror neuron when utilizing a familiar agent (person) with ASD. Similar evidence suggested influence of the individual's own culture, compared to others on modulating the mirror neuron; however, this has never been conducted on an ASD group. Other behavioural data showed that the use of typically developing peers as models in a social intervention setting with ASD was advocated for its significant outcomes, but the impact of age similarity on modulating mirror neurons in ASD children was not directly investigated.

In these two EEG experiments we investigate the effect of observing a person from a familiar age group, and familiar ethnicity group, performing actions, on the capacity of understanding and imitation of others' actions in young children with ASD, compared to a control group.

Participants watched people performing gestures, crossing similarity, of the person's age (child/adult), or of the person's ethnicity (Saudi/European), with familiarity of the action (meaningful/meaningless). Mirror neuron activity, was indexed by theta (5.5-7.5Hz), low mu (9-11Hz), mu (8-13Hz) and low beta (13-20Hz) desynchronization over the sensorimotor cortex. Behavioural performance was recorded through the imitation stage. This is the first experiments to investigate the effect of age and ethnicity on mirror neurons in ASD children, and it showed significant effects for age, and ethnicity, across all bands, supported by behavioural analyses.

Poster Ref: P1-C-003

Theme: C: Sensory and Motor Systems

Non-uniform, non-matching topographies across functional classes of retinal outputs in zebrafish.

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The visual system exhibits topographically ordered maps between connected brain structures that are coherent across functional classes. Our previous work in the zebrafish has revealed two classes of motion-sensitive retinal ganglion cells (RGCs) innervating the optic-tectum that obey different rules during development (Lowe *et al.*, 2013). Orientation-selective (OS) RGCs, which respond to motion along an axis, require visual drive during development to refine their spatial innervation patterns to distributions of four functional sub-types within a tectal lamina. Conversely, direction-selective (DS) RGCs, which respond to motion in one direction only, are not plastic during development and innervate pre-defined laminar segments for each of three sub-types. The consequences of such different developmental rules on retinotopic order are intriguing. Using a Synaptophysin-fused GCaMP3 targeted to RGC axons enabled the spatial receptive fields of axonal terminals within the optic-tectum to be mapped across cumulative populations of OS- and DS-RGCs. We find that whilst DS and OS inputs to the tectum are both retinotopically organised, the OS map is less precise than the DS map at 7 days post-fertilisation. Additionally, the cumulative incidence of DS and OS functional responses are non-uniformly distributed across tectal and visual spaces and exhibit a degree of DS/OS mismatch in visual space.

Poster Ref: P1-C-004

Theme: C: Sensory and Motor Systems

Cellular mechanisms underlying behavioural state-dependent bidirectional modulation of motor cortex output.

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Neuronal activity in primary motor cortex (M1) correlates with changes in behavioural state. However, the cellular mechanisms underpinning behavioural state-dependent changes in M1 output remain largely unresolved. Here we combined *in vivo* patch-clamp recordings, selective pharmacology, projection target mapping and computational modelling to investigate the membrane potential (Vm) dynamics of identified M1 layer 5B (L5B) pyramidal neurons in head-restrained mice during quiet wakefulness and self-paced, voluntary movement.

We show that changing behavioural state – from quiet wakefulness to movement – bidirectionally modulates (i.e. enhances or suppresses) M1 output *via* two opposing subthreshold mechanisms: 1) a global decrease in network-driven, slow large-amplitude Vm fluctuations, which reduced Vm variability, input sensitivity and firing rates in L5Bsuppressed neurons (quiet wakefulness: 6.3±3.9 Hz, movement: 2.8±2.5 Hz, $p<0.001$, n=17); and 2) a coincident increase in excitatory drive to a subpopulation of L5B neurons (L5Benhanced) that depolarised mean Vm, increased input sensitivity and elevated firing rates (quiet: 5.7±3.8 Hz, movement: 12.9±7.4 Hz, $p<0.001$, n=24). The functional classification of L5B pyramidal neurons was not dependent on projection-class identity (pyramidal tract vs. intratelencephalic neurons), suggesting a fundamental organizing principle that transcends projection-type identity.

We next sought to identify the source of the increased excitatory input to L5Benhanced neurons during movement. We found that the movement-related tonic depolarization in L5Benhanced neurons was dependent on the interplay between ascending input from motor thalamus – which maintained Vm near to threshold – and noradrenergic input from the locus coeruleus. The behavioural state-dependent release of noradrenaline mediated a tonic depolarization in Vm and selectively enhanced the signal-to-baseline ratio for information transmission in L5Benhanced neurons (SBR control: 1.1±0.2, SBR following noradrenergic receptor block: 0.3±0.2, $p=0.006$, n=6). Together, our findings provide a mechanism for how noradrenergic neuromodulation and network-driven input changes bidirectionally modulate M1 output during self-paced, voluntary movement.

Poster Ref: P1-C-005

Theme: C: Sensory and Motor Systems

The temporal cortex face expression area, the precuneus, and autism.

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Whole-brain voxel-based unbiased resting-state functional connectivity was analyzed in 396 people with autism and 351 typically developing individuals. We identified a key system in the middle temporal gyrus / superior temporal sulcus (STS) region which has reduced cortical functional connectivity (and increased with the thalamus), which is implicated in face expression and motion processing involved in social behaviour, and which has onward connections to the orbitofrontal cortex/ventromedial prefrontal cortex and amygdala. The same system is implicated in theory of mind processing, and in audio-visual integration for e.g. speech, and possibly in further aspects of communication using language. This system has reduced functional connectivity to face somatosensory and motor areas in the pre- and postcentral cortex, which may normally be used for outputs for such face expression and speech-related processing. This middle temporal gyrus / STS system also has reduced functional connectivity with the orbitofrontal cortex, which may be especially involved in the rewarding aspects of face processing and mentalizing for social communication. We have identified a second key system in the precuneus with reduced functional connectivity which is implicated in spatial functions including of oneself, and of the spatial environment, and suggest that this provides an important contribution to theory of mind processing which is impaired in autism. The findings are consistent with the hypothesis that these two types of functionality, face expression-related, and of one's self and the environment, are important components of the computations involved in theory of mind, whether of oneself or of others, and that reduced connectivity within and between these regions may make a major contribution to the symptoms of autism.

Hasselmo, Rolls and Baylis (1989) The role of expression and identity in the face selective responses of neurons in the temporal visual cortex of the monkey. Behav Brain Research 32: 203-218.

Rolls, Critchley, Browning and Inoue (2006) Face-selective and auditory neurons in the primate orbitofrontal cortex. Exp Brain Research 170: 74-87.

Rolls (2014) Emotion and Decision-Making Explained. Oxford University Press: Oxford.

Poster Ref: P1-C-006

Theme: C: Sensory and Motor Systems

Contextual history influences the rate and neural correlates of motor adaptation in a visuomotor task.

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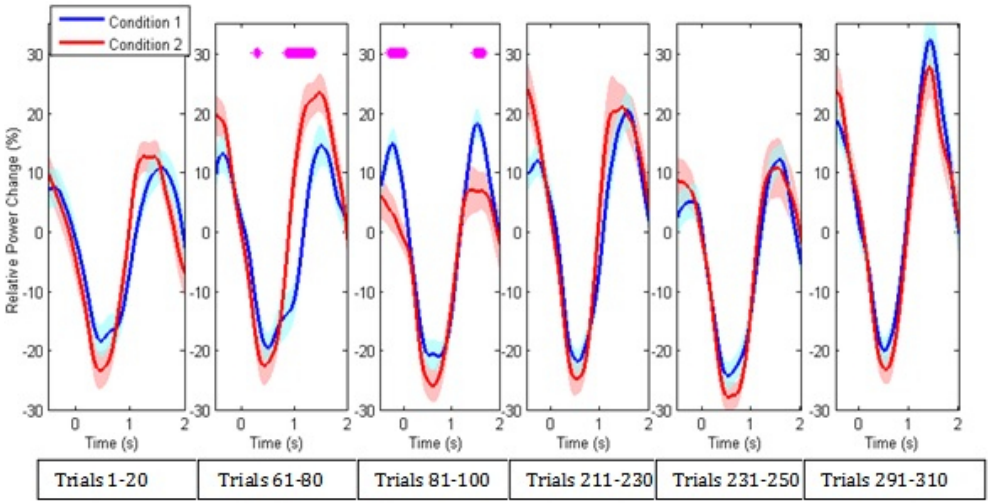
Here we explore the hypothesis that the context of previous performance modulates how movement error impacts on both motor processing and behavioural performance in a task. Recent studies have shown that the power of the post-movement beta-event related synchronisation (PMBS) in contralateral motor cortex (CMC) is dependent upon the size of movement error. The PMBS is increased after a low error trial and decreased after a large error trial. We build on this work by showing that history of the saliency of past errors over multiple trials also modulates the PMBS in CMC.

Eighteen young, healthy subjects undertook a visuomotor joystick adaptation task involving two conditions presented in counterbalanced order. Conditions differed in the angle of perturbation between the joystick and target's movements before an adaptation phase during which perturbation was constant. Condition 1 began with a sequence of random (n=80) perturbations, followed by an adaptation phase (fixed perturbation of 60 degrees, n=150) and then a washout phase without perturbation (n =80). Condition 2 began with a sequence of trials without perturbation (n=80), followed by an adaptation phase (fixed perturbation of -60 degrees, n=150) and then a washout phase without perturbation (n =80). We simultaneously recorded the joystick movement and 12- channel EEG following the international 10-20 system.

We posited that the rate of reduction of error through adaptation with constant perturbations would be slower in condition 1 than in condition 2 due to the initial random perturbation in condition 1, as errors might initially be inferred as non-salient. We further posited that changes in PMBS would similarly be affected.

Our results demonstrated a significant reduction in PMBS between trials 61-80 and 81-100 in condition 2 but not in condition 1. This correlated with a faster rate of adaptation in condition 2 compared to condition 1. Moreover, upon washout, there was no difference in the PMBS or performance between conditions 1 and 2, consistent with the recent experience of more salient motor errors.

These observations suggest that the PMBS reflects neural processes underpinning Bayesian inference of the saliency of prediction error, and hence modulating behavioural performance.



Average beta power across all subjects. At the end of the initial trial sequence (trials 61-80) the PMBS only increased in condition 2, where trials weren't randomly perturbed. Similarly, there was only a drop in PMBS at the beginning of the adaptation phase (trials 81-100) in condition 2, where the significance of movement errors was not obfuscated by the history of earlier random perturbations.

Poster Ref: P1-C-007

Theme: C: Sensory and Motor Systems

Video stimuli reduce object-directed imitation accuracy: evidence from a novel two-person motion-tracking paradigm.

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Imitation is an important form of social behaviour, and research has aimed to uncover the neural and kinematic parameters that underlie imitation. However, much of this research has featured a single participant imitating in response to pre-recorded video stimuli. This is in spite of findings that show reduced neural activation to video versus real life movement stimuli, particularly in the motor cortex. We aimed to discover the degree to which video stimuli may affect the imitation process using a novel motion tracking paradigm with high spatial and temporal resolution. We used 14 motion tracking points to record the hand, arm, and head movements of two individuals in an imitation experiment. One individual freely moved within given parameters (moving balls across a series of pegs) and a second participant imitated. This task was performed with either simple (one ball) or complex (three balls) movement difficulty, and either face-to-face or *via* a live video projection. A cross-correlation analysis of the time-series position data revealed that video feedback resulted in less well correlated and longer latency imitation as compared to face-to-face imitation. We also found that the complex movement task resulted in significantly less accurate imitation than the simple task. This preliminary analysis of our new experiment suggests that video feedback significantly impairs imitation, with important implications for common experimental paradigms within this field. Further, more detailed analyses are underway, aiming to examine joint angles of the arm and grip aperture. We believe that these new methods of experimentation and analysis will deepen our understanding of the kinematic features of human imitation.

Poster Ref: P1-C-008

Theme: C: Sensory and Motor Systems

Thalamocortical axons and deep cortical layer dendritic arbor in motor cortex layer I display a dynamic array of calcium transients during locomotion and systemic blockade of dopamine receptors.

Omar Jaidar, Christopher J. Roome, Yoko Nakano, Marianela Garcia-Munoz, Bernd Kuhn and Gordon W. Arbuthnott

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Thalamus is not only a convergence node it also integrates inputs from basal ganglia, cerebellum and motor related-cortical areas to influence cortical activity. The motor thalamus plays a key role in movement by linking basal ganglia to cerebral cortex. Thalamocortical axons arrive to different areas of cortical layers IV and I. How thalamic activity changes during motor behaviour and how is transferred to other layers in the cortex is not known. The main goal of our research was to visualize *in vivo* layer I activity of thalamocortical axons and dendrites of deeper cortical layer neurons. All our experiments complied with guiding policies and principles for experimental procedures endorsed by the government of Japan. A mixture of AAV1/2-hSyn-GCamP6f and AAV1/2-hSyn-TurboRFP viral vectors was delivered directly into the motor thalamus of 21 days old C57BL/6J mice. Two weeks later, another surgery was performed to place over the motor cortex a chronic cranial window with a silicon access port, as previously described (Roome, C.J. and Kuhn, B. 2014, Front Cell Neurosci. 8, 379, doi: 10.3389/fncel.2014.00379). Two to three days after this last surgery the presence of labeled thalamocortical axons on layer I was confirmed by two-photon microscopy. Then a second injection of AAV1/2-hSyn-GCamP6f in layer V to label neurons and ascending dendritic arbor was delivered using the silicon access port. One week was allowed for viral expression before cortical calcium transients were recorded. A custom-built microscope that combines bright field and two-photon resonance microscopy was used to record calcium transients in head-restrained mice under the following conditions: isoflurane anesthesia, awake and following systemic haloperidol (0.6mg/kg, i.p.).

Layer I axonal activity varies according to the different experimental conditions. In mice awake and moving some axons synchronize their activity during locomotion. During anesthesia axons previously active during locomotion cease their activity and different axons become active and synchronized. Under systemic haloperidol axonal activity exhibits large calcium transients similar to those seen during locomotion mixed with faster and less intense activity.

Poster Ref: P1-C-009

Theme: C: Sensory and Motor Systems

Functional characterisation of transmembrane channel-like protein 1 and 2 mutant mice.

Laura Corns and Walter Marcotti

University of Sheffield

Background: The mechanoelectrical transducer (MET) channel opens in response to stereociliary bundle deflection resulting in an inward current, the role of which is to depolarize hair cells and drive synaptic transmission at their basolateral membrane. There is strong evidence that transmembrane channel-like proteins 1 and 2 (TMC1 and TMC2) play a role in mechanoelectrical transduction (Kawashima *et al.*, J Clin Invest, 121:12; Pan *et al.*, Neuron, 79:1). To date, however, the exact roles of TMC1 and TMC2 have not been established, including the ability of TMC2 to partially compensate for the loss of TMC1 (Kawashima *et al.*, J Clin Invest, 121:12). To further elucidate the relative roles of TMC1 and TMC2 we have investigated the biophysical and pharmacological properties of the MET current in beethoven mice, which have a single point mutation in tmc1, crossed with tmc2 null mice (tmc2Δ/Δ;tmc1bth/bth).

Method: We performed whole cell patch clamp recordings from apical coil outer hair cells (OHCs) of the mouse cochlea. OHCs from tmc2Δ/Δ;tmc1bth/bth mice and littermate controls were studied in acutely dissected organs of Corti from postnatal day 2 (P2) to P14. To elicit the MET current the hair bundles of OHCs were mechanically deflected by using 50 Hz sinusoidal stimuli delivered by a piezoelectric driven fluid jet.

Results: The calcium reversal potential was significantly lower in tmc2Δ/Δ;tmc1bth/bth and tmc2Δ/Δ;tmc1+/bth mice compared to tmc2Δ/Δ;tmc1+/+ control mice. Removing TMC2 alone, however, did not have any effect on the calcium reversal potential in mice of all beethoven genotypes. To further investigate MET channel pore properties, the MET channel blocker, dihydrostreptomycin, was applied to OHCs and was found to be less effective at blocking the MET current in tmc1bth/bth mice than control mice.

Conclusions: Our results suggest that TMC2 is not able to compensate for the defects associated with the tmc1 mutation in beethoven mice. In addition, the reduced calcium reversal potential and reduced block by dihydrostreptomycin in beethoven mice suggest that TMC1 is likely to be the pore forming subunit of the MET channel.

Poster Ref: P1-C-010

Theme: C: Sensory and Motor Systems

Commissural control of ventral lateral and inter-geniculate visual signalling.

Michael Howarth and Timothy Brown

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The lateral geniculate nuclei (LGN) are the primary thalamic target of retinal output and are divided into a dorsal region which supplies the visual cortex and intergeniculate and ventral regions (IGL/vLGN) implicated in circadian and visuomotor control. An import distinguishing feature of the IGL/vLGN is the presence of extensive connections to their counterpart in the opposite hemisphere but the functional roles of these commissural connections are currently unknown.

Using *in vivo* multielectrode recordings from the IGL/vLGN of urethane anaesthetised mice, we found a subset of visually responsive neurons (~15%) that were specifically sensitive to differences in brightness between the two eyes. Electrical stimulation of the IGL/vLGN revealed inhibitory responses in antagonistic cells of the opposite hemisphere exhibiting ipsilateral OFF visual responses and orthodromic excitation of antagonistic cells exhibiting ipsilateral ON responses. Consistent with the notion that ipsilateral components of these antagonistic visual responses were respectively driven by inhibitory and excitatory outputs from the opposing thalamus, antidromically identified commissurally projecting cells, exhibited primarily monocular (contralateral-driven) responses. Moreover, inhibition of commissural signalling, by local infusion of the GABAA agonist muscimol into the opposing IGL/vLGN, reliably converted both types of antagonistic cells into more conventional, purely contralateral driven visual neurons.

In summary these data indicate that commissural communication between ventral portions of the visual thalamus transforms the visual code provide by a subset of neurons, allowing them to report interocular differences in brightness. Given the known role of the IGL/vLGN, we speculate that such cells may play an important role in visuomotor control.

Poster Ref: P1-C-011

Theme: C: Sensory and Motor Systems

Slow irradiance increments scale activity and improve reliability in dLGN.

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Twice a day, at dawn and dusk, we experience a gradual change in background light intensity (irradiance) that covers many decimal orders. A great body of literature has documented the numerous adaptation mechanisms that preserve optimal visual performances across this range. Much less is known about the neural circuits encoding and transmitting such slow irradiance changes. Here, we addressed this problem with *in vivo* extracellular electrophysiological recordings from the mouse visual thalamus (dLGN).

We show that slow increases in irradiance induce widespread increments in firing across the mouse dLGN. Using conventional knockout, chemogenetic, and receptor silent substitution manipulations we show that this response originates with the small population of melanopsin-expressing intrinsically photosensitive retinal ganglion cells (ipRGCs) but influences activity widely across the dLGN. The additional spikes at high irradiance improve the reliability of responses to spatiotemporal visual contrast (where present) and a significant part of this effect can be accounted by a simple multiplicative interaction between irradiance and contrast responses.

Our results highlight two complementary aspects of ipRGCs action. On one hand, gradual increments in firing activity convey information about changing background light intensity. On the other, by scaling firing activity within the early visual system, ipRGCs also improve the reliability of visual responses.

Poster Ref: P1-C-012

Theme: C: Sensory and Motor Systems

Metergoline partially reverses D-amphetamine induced depression of visual activity in the superior colliculus.

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University of Sheffield

Attention deficit hyperactivity disorder (ADHD) is a persistent and debilitating neurodevelopmental disorder which causes impairment across the lifespan. Current estimates show a prevalence rate of ADHD of 5-10% in children and 2-5% in adults with psychostimulant medications such as D-amphetamine used to treat up to two thirds of patients. Though the efficacy of psychostimulant medication in relieving ADHD symptoms has been repeatedly demonstrated, the abuse potential of psychostimulants coupled with the high substance abuse rates associated with ADHD has created controversy regarding their use for treatment of childhood ADHD. Critics of psychostimulants have emphasised the need for development of new non-addictive drugs with similar levels of treatment efficacy, the first step of which is to elucidate the mechanism of action of current psychostimulant medication. One potential therapeutic target of D-amphetamine is the superior colliculus (SC), a midbrain sensory structure which plays an early role in directing attentional resources to distracting stimuli. It has previously been demonstrated that D-amphetamine depresses visual responses in the superficial layers of the SC *in vivo*, which in-vitro evidence has shown to be reversed following local application of a serotonin (5-HT) antagonist. The present study aims to investigate whether D-amphetamine depression of SC visual responses *in vivo* is mediated by 5-HT. We explored the effects of systemic and local introduction of metergoline, a broad spectrum 5-HT antagonist, on SC responses to visual stimuli following systemic application of D-amphetamine. D-amphetamine application resulted in a dose dependent depression of visual activity which was partially reversed by the introduction of metergoline. The results suggest that a focus on 5-HT drugs may be a useful route to developing non addictive therapies for ADHD.

Poster Ref: P1-C-013

Theme: C: Sensory and Motor Systems

In vivo biophysical properties of mature hair cells from the zebrafish lateral line.

Jennifer Olt, Stuart Johnson and Walter Marcotti

University of Sheffield

Hair cells convert sound and balance cues from the outside world into neuronal activity with remarkable precision and fidelity. We currently know a great deal about the development and function of sensory hair cells from *in vitro* studies of animal models ranging from lower vertebrates to mammals. However, we still know very little about how hair cells operate *in vivo*. Larval zebrafish are a popular model for *in vivo* investigations of physiological processes, including the function of sensory receptors in the retina (Dreosti, Lagnado, Exp Physiol. 96:4-12, 2011) and hair cells in the lateral line (Nicolson, Annu Rev Genet. 39: 9-22, 2005). Recently, we have shown that the *in vivo* biophysical properties of hair cells from the lateral line of larval zebrafish (<5days post fertilization, dpf) differ from those obtained *in vitro* from protected fish (>20dpf), which seem to have a higher proportion of mature hair cells (Olt *et al.*, J Physiol. 592: 2041-58, 2014). In order to investigate the physiology of functionally mature sensory cells *in vivo*, we have developed a new experimental approach to record from hair cells and their afferent fibres of >20dpf zebrafish.

Zebrafish were anaesthetized with benzocaine since the commonly used MS-222 has been shown to alter the electrical properties of hair cells (Olt *et al.*, J Physiol. 592: 2041-58, 2014). Benzocaine deeply anaesthetized zebrafish, resulting in muscle relaxation without nociception. Zebrafish >21 dpf were also intubated to guarantee gill oxygenation. Whole-cell patch-clamp recordings showed that benzocaine did not affect the electrical properties or synaptic transmission of hair cells.

Our results provide a crucial methodological advance that will allow *in vivo* recordings from the functionally mature lateral line of the zebrafish in order to investigate mechano-electrical transduction, synaptic transmission and afferent activity.

Poster Ref: P1-C-014

Theme: C: Sensory and Motor Systems

Prostaglandin EP3 receptor activation in the periaqueductal grey differentially regulates spinal processing of A- and C-nociceptor information in the naive and arthritic rat.

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Nociceptive information is transmitted to the spinal cord by peripheral A- and C-nociceptors, which convey different painful sensations and play different roles in the development of nociceptive hypersensitivity following tissue damage. The periaqueductal grey (PAG) is a well-known orchestrator of the descending pain modulatory system that regulates spinal nociceptive transmission and the development of pain hypersensitivity. Within the PAG, prostaglandin E2 signalling has been shown to facilitate spinal nociceptive processing in the naïve and acutely inflamed rat. However, the contribution of prostanergic descending facilitation to nociceptive hypersensitivity in more prolonged inflammation or specifically to secondary hyperalgesia remains unknown. To address these questions we used a pharmacological and electrophysiological approach in naïve and arthritic male Wistar rats which had received an intraarticular knee joint injection of complete Freund's adjuvant (under isofluorane anaesthesia), seven days prior to testing, to induce a secondary hyperalgesia of the hind-paw.

In awake naïve rats, delivery of an EP3 receptor antagonist (GW671021B, 250nM in 300nl) into the ventrolateral (vl) PAG resulted in an increase in withdrawal thresholds to a noxious thermal stimulus. Stereotaxic injection of the EP3 receptor antagonist into the vlPAG of lightly anesthetised rats resulted in a selective increase in the threshold of withdrawal (EMG activity) to preferential C-, but not A-, nociceptor activation in the hind-paw. Arthritic rats developed a secondary hyperalgesia of the hind-paw that was associated with a sensitisation to A-, but not C-, nociceptor activation. In arthritic rats, vlPAG EP3 receptor blockade increased withdrawal thresholds to A- and C-nociceptor activation in the area of secondary hyperalgesia. Additionally, we found that vlPAG EP3 receptor blockade increased the firing threshold of spinal dorsal horn neurones to C-, but not A-nociceptor activation in the area of secondary hyperalgesia. We conclude that EP3 receptor activity in the vlPAG facilitates spinal nociceptive processing of C-nociceptor information in the naïve state and of both A- and C-nociceptor information from the hindpaw area of secondary hyperalgesia during knee-joint arthritis.

Poster Ref: P1-C-015

Theme: C: Sensory and Motor Systems

State-dependent and cell-type-specific functional interactions between basal forebrain and neocortex.

Josue Garcia Yague, Tomomi Tsunematsu and Shuzo Sakata

University of Strathclyde

Cortical states consist of a complex mixture of different oscillatory activities that play different roles in brain functions across a variety of behavioural conditions. The basal forebrain (BF), one of the main neuromodulatory systems, plays a critical role in the cortical state modulation. The BF has been also implicated in attention, motivation, learning and memory, and neurological and neuropsychiatric disorders. The BF contains heterogeneous types of cell populations that differ in their molecular, anatomical, and physiological properties. These include cholinergic, glutamatergic and GABAergic projection neurons as well as different interneurons containing neuropeptide-Y and somatostatin. Because of the heterogeneity in the BF and the complexity of cortical states, however, it still remains poorly understood how diverse populations of BF neurons functionally interact with cortical circuits. In the current study, combining *in vivo* electrophysiological recordings and optogenetic approaches in mice, we firstly characterized how cholinergic and non-cholinergic neurons are active in the BF across different spontaneous cortical oscillatory activities under both anesthetized and non-anesthetized conditions. We found different firing patterns among different BF neurons that correlated with specific oscillatory activities, suggesting functional heterogeneity of BF neurons in cortical state regulation. To further investigate how such state-dependent and cell type-specific firing in the BF is associated with perceptual decisions, we will discuss our results from population activity in both the BF and the auditory cortex during an auditory perceptual detection task, in which near-threshold sounds were presented. Our results could contribute to a better understanding of the mechanisms of cortical state regulation and state-dependent perceptual decision.

Poster Ref: P1-C-016

Theme: C: Sensory and Motor Systems

Input to the brain during active sensation cannot be predicted from passive stimulation: study of whisker system of awake, behaving mice.

Dario Campagner[1], Mathew Evans[1], Michael Bale[1,2], Andrew Erskine[1,3] and Rasmus Petersen[1]

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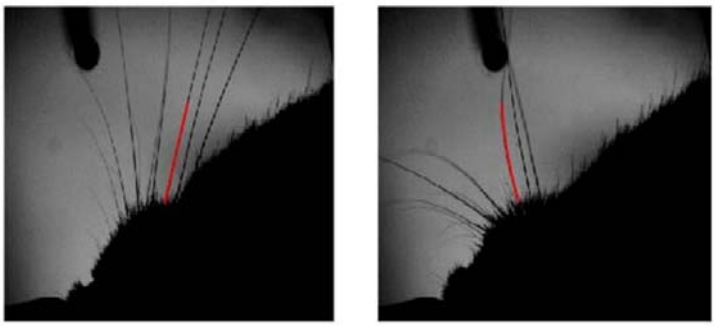
Sensation is active. Animals gain information about their environment by active control of their sense organs. The rodent whisker system is ideal for studying active sensing. Mice explore their world by active whisker movement. Recently, it has become possible to get new insight into the neural basis of active sensation by combining high speed video with electrophysiological recording from awake, behaving mice. The aim of this study was thereby to address the fundamental question of what input the sense organs provide to the brain during natural behaviour.

To this end, we recorded extracellularly the activity of well-isolated, single whisker primary sensory neurons (PSNs) from awake, head-fixed mice as they explored an object (metal pole) with their whiskers. Simultaneously, we measured whisker movements and shape using high speed videography (1000 frames/s, total 1.5M frames). In each frame, we extracted key sensory parameters (whisker angle, whisker curvature, whisker-object contact) using a semi-automatic, custom tracking algorithm.

We found that 90% of recorded units responded to touch and/or to whisking. To determine the sensory parameters that drive the PSN response, we used a Generalised Linear Model (GLM) approach. We fitted GLMs to each unit and tested how accurately the response was predicted based on a variety of sensory inputs. Strikingly, we found that neural responses were often accurately described by a simple GLM , the key input to which was a rotational force (bending moment) on the whisker follicle (correlation coefficient between recorded and predicted response up to 0.91). Conversely, whisker angle was a poor predictor. This unexpected result is in contrast to previous descriptions of angle-encoding derived from passive stimulation in anaesthetised rodents. However, we were able to reconcile these observations by taking into account correlations between bending moment and whisker angle.

In conclusion, we have determined, in awake behaving animals, sensory features that play a major role in driving the activity of whisker primary sensory neurons. These features are different to those previously derived from work in the anaesthetised animals and thereby sheds substantial new light on the nature of active sensation.



Two frames from high speed movie showing mouse whiskers before (left) and during (right) object exploration. Red lines shows the reconstruction of whisker angle and shape (or curvature) automatically operated by the whisker tracking algorithm. Those two values were extracted for each frame and then used to predict the firing of PSNs.

Poster Ref: P1-C-017

Theme: C: Sensory and Motor Systems

BOLD response to auditory object properties in the monkey auditory cortex.

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This work addresses how cues for auditory object perception are represented in the macaque auditory cortex. Previous work suggests that pitch cues are represented beyond the core area A1 in a region that overlaps multiple auditory core and belt fields [PMID 23015424]. Here we address how timbral cues are represented in the macaque auditory cortex: specifically the spectral flux dimension of timbre corresponding to the change in spectrum over time. Previous human work suggests differences in the representation of the timbral property of spectral flux in core and belt homologues [PMID 19052218].

Aims: We sought differences in the relationship between BOLD and r in core and belt cortex.

Methods: Individual core and belt areas were defined on 2 subjects using tonotopic mapping and myelin mapping [PMID 25100930]. We measured the BOLD response corresponding to spectral flux using a synthetic stimulus that affords manipulation of flux independently of bandwidth [PMID 19052218]. Spectral flux was characterised in terms of the Pearson correlation (r) between amplitude spectra of adjacent timeframes.

Sparse EPI images were acquired on a 4.7T upright scanner whilst subjects carried out visual fixation. We acquired 3 runs of stimuli with 5 different r values presented 45 times each in a randomized order. A generalized linear model analysis [SPM8] allowed single-subject inference to determine the relationship between BOLD and r in individual core and belt areas.

Results: In macaque core areas, BOLD activity decreased significantly as a function of increasing r (or decreasing spectral flux). In belt and parabelt, BOLD activity decreased as a function of increasing r with less negative slope than in core.

Conclusions: The data show a difference in the relationship between BOLD and spectral flux in macaque core and belt where the slope becomes more positive between core and belt areas. In the previous human study the slope changed from zero in core homologues to positive in belt homologues (as opposed to changing from negative in macaque core to less negative in belt). Whilst the perception of pitch by macaques appears similar to humans [PMID 25309477] we speculate that different timbre organisation might underlie differences in sounds that are relevant to the two species.

Poster Ref: P1-C-018

Theme: C: Sensory and Motor Systems

Movement intermittency: visuomotor feedback loop or intrinsic rhythmicity?

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In tracking slow targets, humans are known to make periodic intermittent movement with a predominant frequency of 2 Hz, ranging from 1-4 Hz.[1] However, the mechanisms of this low-frequency rhythmicity in behaviour is not fully understood. Previously movement intermittency has been thought to be determined by sensorimotor loop delays, since artificially increasing these delays reduces the frequency of submovements. However, recent work has revealed an intrinsic rhythmicity within motor cortical networks at submovement frequencies around 3 Hz, including during sleep.[2] Therefore we re-examined the possibility of an intrinsic rhythmicity contributing to movement kinematics.

First, we developed a novel 2D bimanual finger force tracking task with a target that followed circular trajectories with frequencies of 0.1 Hz and 0.2. We observed a sharp peak in the power spectrum of the cursor speed at 2 Hz, irrespective of target speed or whether subjects made eye movements or fixated the centre of the screen. Tracking was associated with an increase in delta band (1-4 Hz) power in the electroencephalogram over sensorimotor cortex. This signal was coherent with cursor speed, at around 2 Hz.

To investigate the role of visual feedback, we introduced delays of 100 ms, 200 ms, 300 ms and 400 ms. The main tracking frequency at 2 Hz shifted to a lower frequency as more delay was given. Surprisingly, we observed a second higher frequency peak at twice the main frequency which became more prominent as delay was added. These data could be explained by a simple model in which intermittent movement commands arising from external visual feedback are filtered through motor circuits with intrinsic rhythmicity.

References:

1. Vince MA. Br J Psychol Gen Sect. 1948 Mar;38(Pt 3):149-57.

2. Hall TM, de Carvalho F, Jackson A. Neuron. Sep 3, 2014; 83(5): 1185–1199.

Poster Ref: P1-C-019

Theme: C: Sensory and Motor Systems

Investigating the role of GABAA and glycine receptor inhibition on the rhythmic activity of cultured embryonic rat spinal dorsal horn cells.

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Background: Loss of inhibition in the spinal dorsal horn network in chronic pain conditions has been widely reported. Consequently, GABAA and glycine receptors have been suggested as potential targets for novel analgesics. To investigate the roles of these receptors in the spinal dorsal horn network an *in vitro* model of embryonic rat dorsal horn cells was established. The principal aim of the study is to determine how manipulation of GABAA and glycine receptors affects the spontaneous rhythmic activity of the cultured network.

Methods: The methodology for primary cell culture of dissociated embryonic rat dorsal horn cells was developed. Calcium imaging and multi-electrode arrays were used to measure the activity of the cultured network and how it responds to pharmacological manipulation of GABAA and glycine compounds. Lenti-viral knockdown of glycine receptor alpha subunits is currently being utilized to find how glycine receptor signalling affects the network activity. All animal procedures were performed in accordance with UK Home Office legislation and local regulations.

Results: The spontaneous, synchronous firing of the dorsal horn culture was modulated by application of GABAA and glycine receptor compounds. Antagonists of both GABAA and glycine receptors dose-dependently enhanced firing, these include bicuculline, strychnine and gelsemine. Agonists GABA, muscimol and glycine all decreased firing.

Conclusions: Regulating the inhibitory signalling in the dorsal horn culture has been shown to modify the intrinsic excitability of the dorsal horn network. Altering the firing pattern of the dorsal horn network could be a potential mechanistic target for novel analgesics. These results imply GABAA and glycine receptor compounds are two prospective pharmacological targets that could be used to control this mechanism to produce an analgesic effect.

Research funded as a BBSRC Case studentship with Pfizer Neusentis, UK.

Poster Ref: P1-C-020

Theme: C: Sensory and Motor Systems

The effects of cross-orientation masking on the visual gamma response in humans.

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Introduction: The role of gamma oscillations in visual processing is a topic of ongoing debate. Electrophysiological recordings in primates suggest that visual gamma is not a unitary phenomenon, but instead contains distinct broad- and narrow- band components that reflect different neuronal processes. Evidence from simultaneous multi-unit and gamma-band recordings to grating and plaid stimuli (Bartolo *et al.*, 2011, Eur. J. Neurosci., 34, 1857-70) implies that cross-orientation masking should differentially modulate these two components: narrowband gamma should be greater for gratings while broadband gamma should be greater for plaids. To test this in humans we used MEG to measure the effect of cross-orientation masking on the gamma response.

Methods: We tested twelve participants with five conditions of visually presented stimuli: a luminance-defined plaid stimulus, the two component gratings which formed the plaid and the same two gratings but with Michelson contrast matched to the plaid. Data were recorded using a 275-channel CTF MEG system.

Results: Contrary to our prediction, we found that the amplitudes of both broad- and narrow- band gamma were similarly reduced to the plaid stimulus relative to contrast-matched gratings or to the sum of the two component gratings. We also found that the presence of a cross-orientation mask significantly increased the frequency of narrowband gamma (even when effects of stimulus contrast were taken into account) but did not significantly affect the peak latency of broadband gamma. Surprisingly, we did not find evidence that cross-orientation masking reduced the amplitude of the pattern-onset evoked response.

Conclusions: We have demonstrated that in humans (as in primates) visual gamma is modulated by cross-orientation masking, but we did not find evidence for separable broad- and narrow- band responses. The absence of cross-orientation modulation of the pattern-onset evoked response, but the presence of modulation for the gamma response, suggests that the onset of cross-orientation masking effects occurs between these two responses. This runs contrary to current hypotheses that cross-orientation suppression is generated in thalamocortical inputs to the visual cortex, and therefore warrants further investigation.

Poster Ref: P1-C-021

Theme: C: Sensory and Motor Systems

Electro-cortical therapy for motion sickness.

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Introduction: In light of the increasing popularity of immersive technologies and complex motion environments, the prevalence of motion sickness is set to increase significantly. However, current behavioural and pharmacological therapies are somewhat ineffective (Golding & Gresty, 2005).

Aims: As an intact vestibular system plays a critical role in the development of motion sickness (Golding & Gresty, 2005), we investigate the potential therapeutic benefits from transcranial direct current stimulation (tDCS) used to suppress vestibular function (Arshad *et al.*, 2014).

Methods: We used an off-vertical axis rotation (OVAR) protocol, in which subjects were seated in a motorized chair and were rotated in darkness. Twenty healthy subjects (10M; 10F) were randomly allocated into two age, sex and susceptibility matched groups. Both groups underwent an initial OVAR session during which they were given SHAM-stimulation only. Time taken to self-report: 1) onset of symptoms 2) onset of moderate nausea and 3) self-recovery was recorded. Following a one-hour recovery period, a second OVAR session was performed with unipolar tDCS (either left-cathodal (i.e. test condition) or left-anodal (i.e. control)).

Results: Repeated measures ANOVA for cathodal tDCS stimulation with within-subjects factors: measurement (OVAR duration, first onset of symptoms and time to recovery) and condition (before tDCS, after tDCS) showed a significant interaction measurement*condition ($F= 9.48$, $df=2$, $p = 0.033$) (Figure 1).

Conclusion: Suppression of vestibular cortical function with cathodal tDCS results in subjects exhibiting enhanced tolerance for motion sickness. We propose this technique provides a novel approach for the future treatment of motion sickness.

References

Arshad, Q., Nigmatullina, Y., Roberts, R. E., Bhrugubanda, V., Asavarut, P. & Bronstein, A. M. (2014) Left Cathodal Trans-Cranial Direct Current Stimulation of the Parietal Cortex Leads to an Asymmetrical Modulation of the Vestibular-Ocular Reflex. Brain Stimulation. 7 (1), 85-91.

Golding, J. F. & Gresty, M. A. (2005) Motion sickness. Current Opinion in Neurology. 18 (1), 29-34.

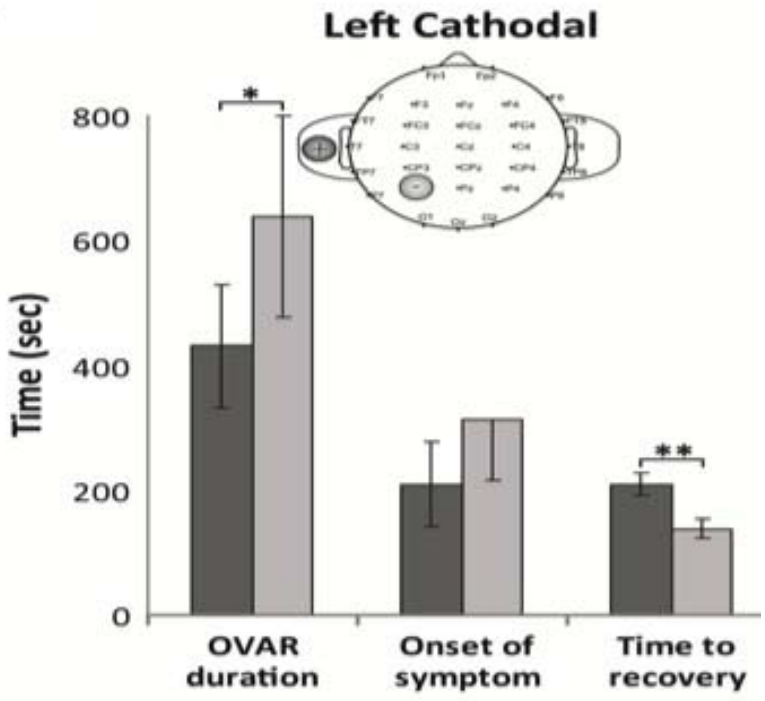

Figure 1. Effects of electro-cortical stimulation on motion sickness susceptibility. Following left-cathodal tDCS, there is a significant increase in OVAR duration to induce moderate nausea and significant reduction of the time taken to symptom recovery. Error bars represent standard errors. *indicates $p < 0.05$ and ** indicates $p < 0.01$.

Poster Ref: P1-C-022

Theme: C: Sensory and Motor Systems

The evaluation of pain in amyotrophic lateral sclerosis.

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[1]Kings College London, Institute of Psychiatry, [2]The Motor Nerve Clinic, Academic Neurosciences Centre, Kings College Hospital, London

Introduction: Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease leading to paralysis. As ALS progresses, secondary symptoms develop including pain. Pain has been a poorly studied and poorly managed feature of ALS and further information is required to aid better clinical recognition, management and research into efficacious therapies.

Aims and Objectives: This study aims to provide evidence on the prevalence, severity, nature and impact of pain in ALS.

Methods: Ethical and R&D approval was gained prior to the study. People with ALS attending a specialist multidisciplinary clinic were invited to participate. Their relatives participated as healthy controls. Data was obtained using the Brief Pain Inventory and Pain Detect questionnaires.

Results: Pain was reported by 85% of those with ALS (n=41) vs 35% of controls (n=42). 97% reported pain for at least 6 months. The most common locations for pain in ALS were legs, arms, shoulders, neck & back. The most common types of pain were: cramping, aching, tiring, sharp and tender. Pain significantly interfered with activity levels, mood, sleep, relationships, and enjoyment of life. There was a significant correlation between pain score and interference levels. The type of pain described was nociceptive in nature with no neuropathic component.

Conclusion: Pain is a significant symptom associated with ALS that is present throughout the course of the disease. Pain interferes significantly with quality of life and it is therefore important that pain is addressed as part of the routine management of this devastating disease.

Poster Ref: P1-C-023

Theme: C: Sensory and Motor Systems

A passive touch experiment using steady-state evoked potentials to tag the cortical activity related to the perception of natural textures.

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When sliding our fingertip on a surface, complex vibrations are produced in the skin. In the present study we examined whether the sustained cortical activity generated by the mechanical interaction between the finger pad and a sinusoidal grating can be captured in the form of a steady-state evoked potential (SS-EP). The electroencephalogram (EEG) was recorded using 64 channels. During the recording, the right index fingertip was passively scanned against a sinusoidal plastic plate with a 3.52 mm spatial period (SP), using a constant normal force (1.5 N) and a constant exploration velocity (17.6 mm/s). The movement of the grating was achieved using a robot with a feedback force sensor. The grating was presented with and without a polyester fabric glued on the surface, resulting in two conditions. Frequency analysis of the recorded EEG signals showed that modulation of the vibrations induced by fingertip/texture interactions induced an SS-EP at the frequency of modulation (5 Hz) as well as its first harmonic (10 Hz). The amplitude of the elicited brain response was maximal over the hemisphere contralateral to the stimulated side. Whereas the two stimuli elicited a similar response at 5 Hz, only the grating with the polyester fabric elicited a significant response at 10 Hz. Taken together, our results suggest that SS-EPs could be used to isolate and study the brain responses related to the tactile exploration of textures.

Poster Ref: P1-C-024

Theme: C: Sensory and Motor Systems

Cortical local field potential power is associated with behavioural detection of near-threshold stimuli in the rat whisker system: dissociation between prefrontal and somatosensory cortices.

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University of Leicester

There is growing evidence that prefrontal top-down control of sensory areas may represent a key regulator of attentional processes and as such may contribute to behavioural performance in psychophysical tasks. However cortical dynamics may differentially regulate sensory detection vs. discrimination. Here we used the rat whiskers as a model system to further characterize the relationship between cortical state and tactile detection. Head-fixed rats were trained to report the presence of a vibrotactile stimulus (frequency 60Hz; duration 2 sec; deflection amplitude 0.01-0.5 mm) applied to a single vibrissa. We calculated power spectra of local field potentials preceding the onset of near-threshold stimuli from microelectrodes chronically implanted in orbitofrontal and somatosensory cortex. Stimulus detection was associated with decreased delta power in orbitofrontal cortex and increased delta power in barrel cortex. Further, coherence between prefrontal cortex and barrel cortex was reduced in successful detection trials. Consistent with previous work suggesting a trade-off between brain dynamics mediating behavioural detection *vs*. discrimination, these results provide direct behavioural evidence of a dissociation between prefrontal and sensory cortical mechanisms of detection in the rodent tactile system.

Poster Ref: P1-C-025

Theme: C: Sensory and Motor Systems

Laminar-specific temporal profiles of state-dependent stimulus encoding in rat auditory cortex.

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Activity in the absence of stimuli is ubiquitous across the thalamocortical system (TS), with patterns of spontaneous activity reflecting ongoing behavioural state. Under anaesthesia and during deep sleep the TS operates in an inactivated state (characterised by low frequency high amplitude oscillations in local field potential (LFP)) in which neurons collectively alternate between periods of local silence and high synaptic activity. During wakefulness and REM sleep, however, the TS operates in an activated state (characterised by high frequency low amplitude oscillations in LFP) in which neurons fire in a sustained desynchronised manner. Such brain states may be indicative of different modes of neural processing, but the effect of brain state on neural processing remains unclear.

Here we analyse data recorded in the auditory TS of urethane anaesthetised rats subjected to single-click auditory stimulation over a range of intensities, presented in both the inactivated state (natural under the anaesthesia) and the activated state (induced through electrical stimulation of the basal forebrain). Evoked spike trains were identified for single units in the auditory thalamus and across depths of the primary auditory cortex. Mutual information (MI) between stimulus and response was then computed for spike response probability, counts and timing.

Multiunit evoked activity was observed to last around 300ms, consisting of distinct initial and secondary (rebound) activity. Analysis of responses of single units over the full 300ms window showed that spike count and timing measures gave little more MI than response probability, suggesting that stimulus intensity is primarily encoded probabilistically, at least at the level of the single unit. Moreover, whilst many single units are uninformative of stimulus intensity, informative thalamorecipient (TC) and infragranular (IF) single units show increased MI in the activated state. Additionally, upon temporally partitioning data according to initial or rebound activity, we see that the the former result holds for TC units only in the initial activity and for IF units only in the rebound activity, suggesting that information loss in the inactivated state may be cumulative in time as sensory signals propagate through neural circuits.

Poster Ref: P1-C-026

Theme: C: Sensory and Motor Systems

Lipopolysaccharide-induced production of pro-inflammatory cytokines in trigeminal ganglion neurons *via* Toll-like receptor activation.

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[1]School of Biomedical & Healthcare Sciences, Plymouth University, [2]School of Dentistry, Plymouth University

Recent interest has focused upon the expression of Toll-like receptors (TLRs) on sensory neurons. The direct expression of TLRs on high-threshold dorsal root and trigeminal ganglion (TG) sensory neurons (nociceptors) permits direct interaction between neuron and pathogens. The activation of TLR4 on trigeminal neurons has been shown to potentiate TRPV1 heat-evoked responses and TRPV1-dependent neuropeptide release. In the dorsal root ganglion, activation of neuronal TLR4 induces the production of multiple inflammatory mediators however LPS-induced inflammatory mediator production in TG neurons is currently unknown. Here we investigate changes in pro-inflammatory gene expression of rat TG neurons, *in vitro*, in response to challenge with *E. coli*- and *P. gingivalis*-derived lipopolysaccharide (LPS).

Freshly dissected trigeminal ganglia were enzymatically and mechanically dissociated and spun through a 30%/60% Percoll gradient. The neuron-containing layer was harvested and cultured for 48 hours in growth-factor free media prior to LPS exposure (1µg/mL, 2 hours). Changes in TNFα, IL-1β, IL-6 and IFNβ gene expression were measured by qPCR using GAPDH and β-actin as endogenous controls.

Following 2 hour exposure to *E. coli* LPS (1µg/mL) TNFα and IL-1β gene expression increased by 11.85±2.21 and 5.99±0.31 fold, respectively, relative to endogenous controls (n=3). In contrast there was no significant change in gene expression levels of IL-6 or IFNβ. The gene expression data for *P. gingivalis* LPS exposures are currently under investigation.

We and others have previously shown nociceptor specific expression of TLR4 within TG sensory neurons. Here we show that LPS induces the neuronal expression of two pro-inflammatory cytokines which are known to increase neuronal excitability. The induction of TNFα and IL-1β suggests that neuronal TLR4 signals through the MyD88-dependent pathway following LPS exposure. Overall our results suggest that neuronal TLR4 activation by LPS contributes towards the establishment and maintenance of heightened pain states associated with bacterial infections, albeit by currently unresolved mechanisms.

Poster Ref: P1-C-027

Theme: C: Sensory and Motor Systems

Effects of pleasant and unpleasant odours on hedonic evaluations of human faces: an event-related potential study.

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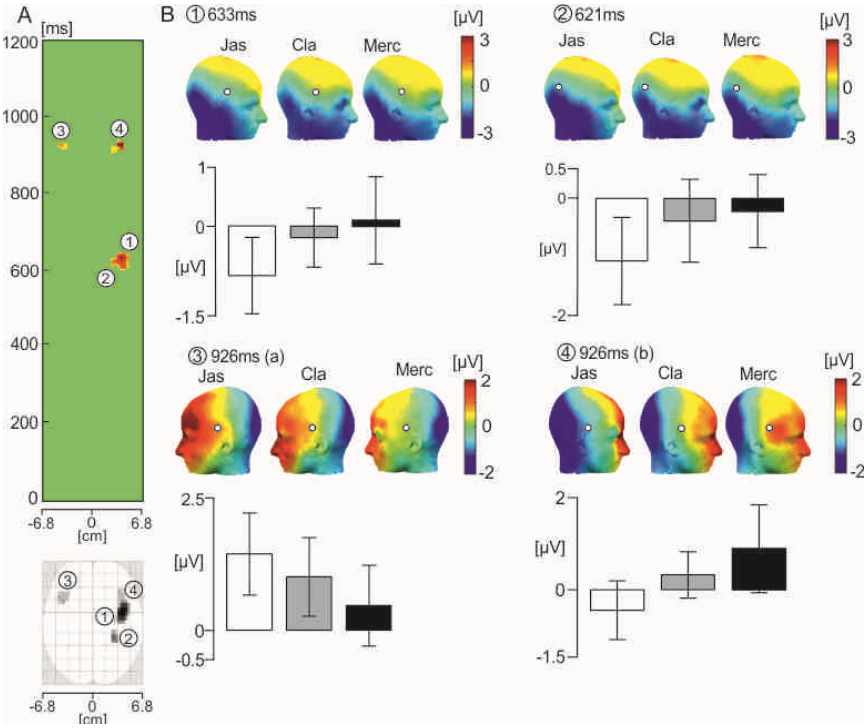
Odours have been shown to alter hedonic evaluations of objects and human faces. The present study aimed to analyse the neural underpinning of odour-induced changes in hedonic evaluations of human faces in an affective priming paradigm using event-related potentials (ERPs).

Twenty healthy males and females rated emotionally neutral male and female faces presented 1 s after a 3-s pulse of either a pleasant (jasmine) or unpleasant (methylmercaptan) odour, or a no-odour control (clean air). EEG was recorded continuously using a 129-electrode system.

Neutral faces presented after administration of the pleasant odour were rated significantly more pleasant than the same faces presented after administration of the unpleasant odour (and control). Analysis of face-related potentials revealed four clusters of electrodes significantly affected by odour condition at specific time points during the late positive potential (600-950 ms). In the 620-640 ms interval, two scalp-time clusters showed a greater negative potential in occipital and posterior temporal-parietal electrodes in response to faces in the pleasant odour condition in comparison those in the unpleasant odour condition. At 926 ms, face-related potentials showed greater positivity in response to faces in the pleasant and unpleasant odour conditions in the left and right lateral frontal-temporal electrodes, respectively.

Odours alter hedonic evaluations of human faces even if targets follow odour primes after a slight temporal lag. Odour-induced shifts in hedonic evaluations of neutral faces are associated with amplitude changes in the late (>600) and ultra-late (>900 ms) latency epochs. The ultra-late component disentangled effects of pleasant and unpleasant odours consistent with right-hemisphere preponderance for unpleasant and left-hemisphere preponderance for pleasant odours, and subsequent affective responses.



Effect of three odour conditions on face-ERPs.

A. A green panel shows four numbered clusters where there was a significant effect of odour condition in a scalp-time plot, with a standard scalp map below displaying these clusters in the brain. B. Topographic maps of significant cluster latencies under each odour condition, with bar graphs below illustrating the mean EEG amplitude.

Poster Ref: P1-C-028

Theme: C: Sensory and Motor Systems

Dissecting function and genetics of circuits controlling goal oriented movements.

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MRC Laboratory of Molecular Biology, Cambridge

Goal-oriented movements require the ability to use available sensory and perceptual information to generate spatially tuned movements. Nearly all we know about goal-oriented movements in mammals derives from studies on primates and cats. However, due to the limitations of such non-genetically-amenable models, these populations are exclusively characterised on the basis of their anatomical location and firing properties. We used a multi-level approach to investigate the premotor circuits controlling the movement of the head in mice. The sensory-motor transformation that leads to head displacement arises in the superior colliculus (SC). We moved form *in vitro* preparations to *in vivo* study to dissect the intrinsic properties, the circuit design and genetics of neurons involved in the control of goal-oriented movements. Firstly, we characterised the electrophysiological properties of neurons in the deep layers of the SC *in vitro*. Secondly, by taking advantage of mouse genetics we assigned a precise genetic identity to one of such classes. Thirdly, we focussed on the functional role of neurons in the deep SC *in vivo*; to understand whether the activity of these neurons promotes spatially tuned movements and whether the metrics of motion obey to a topographic organization. We recorded neural activity of deep SC neurons *in vivo*, in freely moving mice and in a 'head-free' multisensory virtual reality environment. Using a custom-built sensor we quantitatively measured three dimensional head displacements in real time in freely moving animals and correlated single units activity with the produced head displacement vectors. In parallel we also characterised the produced motor output upon optogenetic activation of deep SC neurons. We found that the activity of deep collicular neurons correlates with specific head displacement vectors and that their optogenetic activation induces spatially tuned head displacements; the metrics of the recorded or induced displacements vary with the location of the stimulation site. We are currently investigating the kinematics of the produced motor responses as a function of the genetics heterogeneity of the involved neuronal populations.

Poster Ref: P1-C-029

Theme: C: Sensory and Motor Systems

Knockdown of HCN1 channels in the inferior olive results in motor behaviour deficits.

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University of Edinburgh

Molecular mechanisms that configure neuronal responses to synaptic input are critical for coordinated behaviour. Evidence from mice with global deletion of the HCN1 gene, which encodes hyperpolarization-activated cyclic nucleotide-gated (HCN) channels with rapid kinetics, suggests that this channel is important for synaptic integration underlying learned motor behaviours. However, while HCN1 is strongly expressed in cerebellar Purkinje cells, deletion of the channel solely from these neurons is not sufficient to account for behavioural deficits in mice with global deletion of HCN1. An alternative possibility is that HCN1 channels strongly expressed by neurons in the inferior olive mediate behavioural deficits in HCN1 knockout mice. To address this we investigated effects of knockdown of HCN1 in the inferior olive (IO) using AAV co-expressing EGFP to label transduced neurons and interfering RNAs targeted against HCN1. EGFP expression was found in the IO and transduction of neurons expressing HCN1-miRNA resulted in a hyperpolarized resting membrane potential, an increase in input resistance, and a reduction in the voltage sag generated by a hyperpolarizing current compared with neurons expressing miRNA targeted to a control Luciferase sequence. To test the effect of the HCN1 knockdown in the IO on motor output we used an accelerating rotarod test. Four weeks after AAV injections, mice were trained on the accelerating rotarod (4-40 rpm in 300 s) for four sessions *per* day, during four days. On the fifth day mice were tested at constant rotation speeds ranging from 5 to 30 rpm. Mice injected with HCN1-miRNA-AAV (n = 19) performed worse throughout the first four days of testing than mice injected with Luciferase-miRNA-AAV (n = 14, p = 0.024, ANOVA). On the fifth day HCN1-miRNA-AAV injected mice performed worse at 5 rpm but not at higher speeds. These data suggest that HCN1 channels in the IO are important for motor learning. To address the mechanism for this role of HCN1 we are now investigating how HCN1 channels in the IO affect neuronal activity in the cerebellar cortex of awake behaving mice.

Poster Ref: P1-C-030

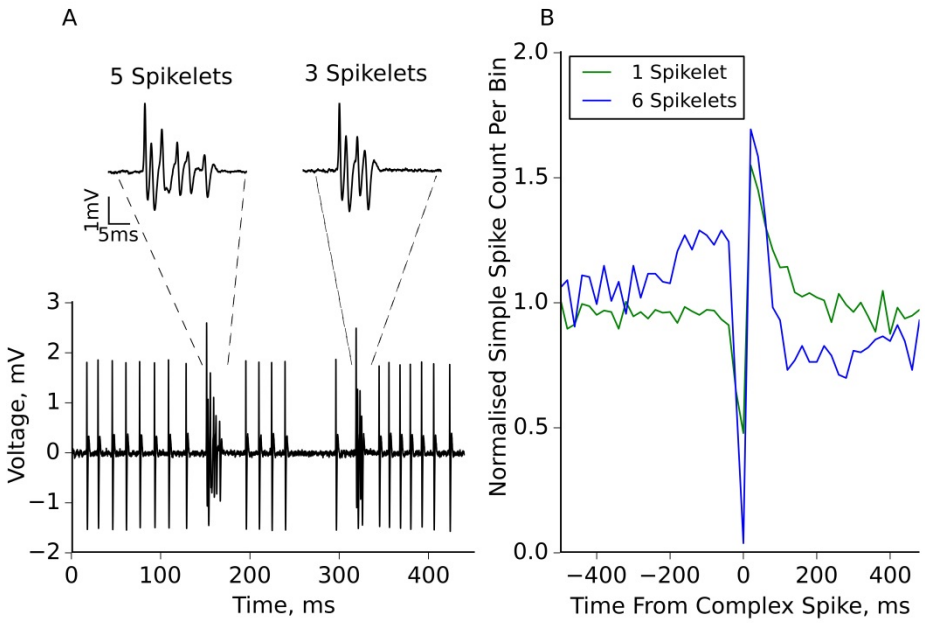
Theme: C: Sensory and Motor Systems

Dynamic interplay between simple spike activity and complex spike waveform in cerebellar Purkinje cells.

Amelia Burroughs[1], Nadia Cerminara[1], Andrew Wise[2], Conor Houghton[1] and Richard Apps[1]

[1]University of Bristol, [2]Bionics Institute, Melbourne, Australia

Cerebellar activity is critical for motor control and coordination and is necessary for learning movements. The Purkinje cell (PC) is the only neuronal type to project out from the cerebellar cortex and influence downstream motor processing, *via* cerebellar and vestibular nuclei. Purkinje cell spike trains must therefore represent all computations performed within the cerebellar cortex. Purkinje cells fire two distinct types of action potential: simple spikes and complex spikes. Simple spikes are stereotypical, sodium-mediated action potentials that can be elicited intrinsically (~30Hz). Complex spikes are infrequent (~1Hz) and are evoked by climbing fibre input. Complex spikes are composed of an initial large spike that is then followed by a number of secondary components, termed spikelets. The number of spikelets comprising the complex spike waveform varies. Interactions between simple spikes and complex spikes within the same Purkinje cell have been extensively studied, however most of these investigations have considered complex spikes as unitary events. The extent to which differences in complex spike spikelet number affect simple spike activity (and *vice versa*) remains unknown. In ketamine/xylazine anaesthetised adult rats (n=10 rats), we have found that high simple spike firing frequencies precede complex spikes with greater numbers of spikelets, but following the complex spike event the simple spike rate is reduced (n=28PCs). This depression is observed after all complex spikes, but is graded with spikelet number. We therefore suggest that the complex spike waveform may act to maintain intrinsic simple spike firing frequency. Furthermore, simple spike firing rate appears to cluster complex spike waveforms. It is possible that these distinct waveform-types mediate specific aspects of cerebellar operation and ultimately motor behaviours.



Example extracellular Purkinje cell recording (A) shows 2 complex spikes with different numbers of spikelets (5 and 3) occurring close in time. Peri-event time histograms (B) illustrate how simple spike activity around the time of a complex spike event varies with spikelet number (20ms bins, green=1 spikelet (n=981CSs), blue=6 spikelets (n=384CSs). Complex spikes may regulate simple spike firing.

Poster Ref: P1-C-031

Theme: C: Sensory and Motor Systems

Mapping the internal geometry of tactile space.

Matthew Longo and Olga Golubova

Birkbeck, University of London

Recent research has revealed large anisotropies of tactile distance perception, with distances oriented across the width of the arms being perceived as bigger than those oriented along arm length. In this study, we investigated the spatial organisation of tactile distance judgments in a more holistic way, reconstructing a metric representation of the underlying space of tactile judgments. We used multidimensional scaling (MDS) to reconstruct 2-D maps of the perceived structure of the tactile space of the hand. Participants made verbal judgments of the perceived distance between two successive tactile stimuli presented to the hand dorsum. Across trials, every possible pair of 16 points arranged in a 4x4 grid was stimulated. MDS was applied to the resulting distance matrix for each participant to produce a perceptual map of tactile space. These maps were systematically distorted, being stretched along the width of the hand. This distortion was well characterised by a simple affine stretch applied to tactile space. Subsequent experiments showed that the magnitude of distortion was reduced on the palmar hand surface and that the distortion exists in a hand-centred frame of reference. These results demonstrate: (a) that tactile spatial perception relies on a highly-structured spatial field, (b) that this field is systematically distorted, (c) that this distortion can be characterised by a mathematically simple deformation of actual skin space, and (d) the distortions are specific to 2-D skin surfaces rather than the hand as a 3-D object.

Theme D: Learning, Memory and Cognition

Posters P1-D-001 to P1-D-062

Poster Ref: P1-D-001

Theme: D: Learning, Memory and Cognition

Local LTP induction modulates global network activation patterns: an fMRI perspective.

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Rationale: The possibility that experimentally induced synaptic potentiation, in addition to causing local changes, could trigger wider network alterations is relevant to hippocampal-neocortical interactions in memory processing. This project, involving combined *in vivo* electrophysiology and functional Magnetic Resonance Imaging (fMRI) experiments, focused on CA3-CA1 synapses and downstream extrahippocampal communications.

Method: Sprague-Dawley rats (n=15) were used, with electric microstimulation of the Schaffer collaterals or CA3 pyramidal cell layer and subsequent monitoring of the activation pattern using both multichannel electrophysiology recordings and fMRI imaging (7 Tesla). We investigated the effects of a range of stimulation frequencies (5, 10, 20 and 40 Hz) and intensities (500 and 800 uA). Local activation patterns increased monotonically with applied intensity, but frequency modulation followed a biphasic pattern. Whilst activity within the hippocampal formation increased gradually with higher frequencies, the extrahippocampal spreading of activity was only seen at 10 and 20 Hz giving an inverted U-shaped function. Induced synaptic potentiation modulated the extrahippocampal spreading, allowing greater propagation at 5 and 40 Hz.

Interpretation: These results identify frequency-dependent information channels in brain-wide networks that appear to fulfill the dual needs of local independency and global integration through segregating activity propagation in the frequency domain.

Supported by grants to SC from the Spanish MINECO (BFU2012-39958). The Instituto de Neurociencias is a "Centre of Excellence Severo Ochoa". AM is supported by a studentship from the Univ. Edinburgh, and RM by a Royal Society International Exchange Grant and by the European Research Council.

Poster Ref: P1-D-002

Theme: D: Learning, Memory and Cognition

Difference in behavioural expression of hippocampal and cortical memory trace.

Lisa Genzel, Janine Rossato, Justin Jacobse, Richard Fitzpatrick and Richard GM Morris

CCNS, University of Edinburgh

Background: For memory traces to be successfully recalled, they need to be consolidated. Different factors are thought to influence this process including (1) novelty exposure that enhances the persistence of a hippocampal trace *via* neuromodulation; and (2) sleep that aids systems consolidation and thus a cortically based memory. Do such hippocampal and cortical and traces differ qualitatively with respect to their behavioural expression, or their persistence over time? To investigate this, rats were trained on two competing memories with training to one followed by sleep deprivation plus novelty (hippocampal) and the other by sleep (cortical), followed by different interference protocols.

Methods: In Expts. 1 through 4, rats were trained to learn two opposite escape locations in a watermaze over 2 sessions, with novelty + sleep deprivation, or sleep following session 1 and the alternative intervention after session 2 (counterbalanced). Probe trials without any platform present were conducted at varying times afterwards (Expt 1: 24h, 7d and 21d (within-subjects); Expt 2: 7d and 21d). In Expt 3, rats will experience a third platform location at 24h to investigate the effect of active interference and in Expt 4 the rats will be pre-exposed to the water maze environment before the training day.

Results: Current results (Expts 1+2) showed that in probe tests at 24h, the rats remembered both escape locations in the watermaze, but displayed a preference for the location whose encoding was followed by novelty (hippocampal trace dominating). This hippocampal memory trace did not survive to 7d at which time the cortical trace dominated. In Expt 2 without the 24h probe, the novelty-enhanced memory trace did survive, suggesting the expression of a hippocampal trace can contribute to its demise. Performance was at chance in all conditions by 21d. Expts 3 and 4 are underway.

Conclusion: These data contribute to other findings suggesting a dynamic interplay of hippocampal and cortical memory. They indicate that cortical memory is more resistant to interference, but at the cost of being less exact and vivid, while hippocampal memory can enable a stronger behavioural response soon after memory encoding.

Supported by ERC and Branco Weiss Society in Science Fellowship.

Poster Ref: P1-D-003

Theme: D: Learning, Memory and Cognition

Differential involvement of GABA, NMDA and AMPA receptors in spatial memory encoding and retrieval.

Janine I Rossato and Richard GM Morris

CCNS - University of Edinburgh

Background: The hippocampus has long been implicated in the encoding, consolidation and retrieval of place memory on the basis of lesion and electrophysiological studies. Such memory relies on the rapid encoding of allocentric relations among multiple cues such that goals can be approached from different positions. However, it is likely that excitatory and inhibitory neurons, and distinct receptors, contribute to hippocampal memory processing in dissociable ways. The aim of this study was to explore this idea using an 'everyday' memory task in which new place memories are formed each day.

Methods and Results: The delayed matching-to-place (DMP) paradigm in the watermaze was used. Over a period of up to 21 days, Lister hooded rats (n=12) were given 4 daily trials to an escape platform hidden in a new location each day, with the memory interval (ITI) of 20 min between trials 1 and 2 (15 sec thereafter). Critically, bilateral intrahippocampal drug infusions were given on the second of successive 'blocks' of 3 training days (the GABA-A agonist muscimol (MUS), the NMDA antagonist D-AP5 or the AMPA receptor antagonist CNQX). Findings to date indicate that muscimol prevents on Day 2 successful memory retrieval of the location encoded on Day 1, but not the learning of a new platform position as the Day 2 location is remembered on Day 3. Our predictions are that (a) CNQX on Day 2 will also inhibit retrieval of the Day 1 location, but additionally prevent learning on Day 2 and thus memory on Day 3; and (b) D-AP5 will have no impact on memory retrieval on Day 2, but also prevent learning. CNQX and D-AP5 may allow successful memory of the Day 1 location on Day 3.

Discussion: The differential effects of these distinct forms of hippocampal interference likely reflect GABAergic effects that block cell firing, while leaving excitatory EPSPs and NMDA receptor activation intact (muscimol); blocking EPSPs and consequently both retrieval and new learning (CNQX); blocking NMDA receptor activation and thus learning but not retrieval (AP5).

Supported by ICT-FET Grant GRIDMAP.

Poster Ref: P1-D-004

Theme: D: Learning, Memory and Cognition

Spaced access to food reward produces more persistent memory in an everyday spatial memory task.

Mio Nonaka[1], Richard Fitzpatrick[1], Marco Peters[2] and Richard GM Morris[1]

[1]University of Edinburgh, [2]DART Neuroscience

Rationale: Comparisons of massed vs. spaced trials reveal an advantage for spaced training in numerous appetitive and fear-conditioning tasks in rodents, including object recognition memory. Studies of odorant fear conditioning in Drosophila suggest trial-spacing may preferentially activate CREB and induce better long-term memory, pointing to a possible route towards the design of cognitive enhancing drugs (Tully *et al*, Nature Rev. Drug Discovery, 2003).

Methods: Using an appetitive 'everyday' spatial-memory task in an event arena in which the location of reward changes daily, we investigated the impact of the spacing access to reward within the daily 1-trial learning protocol. Lister-hooded rats (n = 23) were trained to dig in sandwells (SW) to find food. At daily 'sample' trials (memory encoding), there were 2 SWs – only one containing reward (1-5 pellets). In daily 'choice' trials (memory retrieval), there were 6 SWs of which only the initially rewarded SW was again rewarded. In occasional choice probe tests (memory retrieval), none of the SWs had food and we measured preferential digging amongst the choices as an index of memory. Our key finding is that spacing access to 3 successive rewards from 30 sec to 10 min within a sample trial resulted in a stronger memory that was persistent for 24 h. Post-training novelty, scheduled 30 min after the daily encoding trial (which should upregulate plasticity-related protein synthesis), improved the discriminability of SW choices within a probe trial.

Implications: This 'everyday' task has great potential as a test of the strength and persistence of the types of memories we make and lose on a daily basis. This greater validity to real-world memory may enable better predictive translation to humans of putative cognitive enhancing drugs (see Neuron, 5 Nov 2014), such as phosphodiesterase 4 inhibitors.

Supported by DART Neuroscience.

Poster Ref: P1-D-005

Theme: D: Learning, Memory and Cognition

Electrophysiological change induced by Gi-DREADD treatment in PP-DG EPSP waveform and spikes.

Mio Nonaka and Richard GM Morris

University of Edinburgh

Phermacogenetic tools such as DREADD (Designer Receptors Exclusively Activated by Designer Drugs), developed by Bryan Roth Lab, would be useful tools to intervene neural activities in defined neuron types in specific regions of the brain in a reversible manner. With a highly efficient AAV infection, we aimed to use one of the DREADD systems, Gi-DREADD system, to inhibit a brain structure as large as rat dorsal hippocampus. Gi-DREADD is reported to work by suppressing the glutamate release of the neurons expressing hM4D (Stachniak T.J. *et al.*, 2014), thus by inhibiting the activity of the downstream neurons, and could be a promising brain region specific activity inhibition method with several advantages over cannula mediated drug infusion, such as less intervention, better cell specificity and traceability of the neurons modulated.

Here we set out to characterize the electrophysiological effect of Gi-DREADD treatment in the dentate gyrus (DG) of the rat brain. We injected AAV8-CaMKII-hM4D bilaterally into the DG of the wild-type Lister-hooded rats and 3 weeks later we recorded LFP and spikes in the DG evoked by ipsilateral perforant path (PP) stimulation. Intraperitoneal injection of clozapine-N-oxide (CNO, an agonist for the hM4D) induced an increase in the spike amplitude and a small change in the EPSP waveform that lasted for more than 4 hrs. To verify this effect and to accelerate the onset and clearance of CNO, we infused CNO into the ventricle through a cannula. This CNO infusion resulted in a large increase in the spike amplitude as well as a drastic change in the waveform of PP-DG EPSP.

This seemingly contrary effect to what was expected for Gi-DREADD might suggest that there is a strong feedback system within the DG or downstream of DG granule cells to regulate the EPSP and the spikes.

Supported by ERC and JSPS (Japan Society for the Promotion of Science).

Poster Ref: P1-D-006

Theme: D: Learning, Memory and Cognition

Optogenetically identified catecholaminergic neurons in mouse ventral tegmental area and locus coeruleus are activated by novelty.

Adrian Duszkiewicz[1], Tomonori Takeuchi[1], Patrick Spooner[1], Karl Deisseroth[2] and Richard Morris[1]

[1]Centre for Cognitive and Neural Systems, University of Edinburgh, [2]Department of Bioengineering, Stanford University, USA

Rationale & Aim: The synaptic tagging-and-capture (STC) theory of initial memory consolidation holds that memory persistence can be altered by prior or subsequent patterns of neural activity. Our laboratory has previously shown that 5-min exploration of novel environments can facilitate persistence of unrelated spatial memories encoded around the same time. This phenomenon is blocked by antagonists of D1/D5 dopamine receptors in the rodent hippocampus (Wang *et al.*, PNAS, 2010; Takeuchi *et al.*, BNA 2013 abstract), but the source of dopamine that mediates the effect of novelty on memory persistence has not yet been identified. An influential model of initial memory consolidation points to the critical role of catecholaminergic (CA) neurons in the ventral tegmental area (VTA) (Lisman *et al.*, TINS, 2011), but recent evidence also implicates locus coeruleus (LC) as a potential source of dopamine in the hippocampus (Smith and Greene, J. Neurosci., 2012). We performed optetrode recordings from optogenetically identified CA neurons in mouse VTA and LC during exploration of novel and familiar environments in order to establish which CA nuclei are activated by novel experiences.

Methods: Using tyrosine hydroxylase-Cre mice and a Cre-dependent adeno-associated viral vector, we tagged CA neurons in VTA and LC selectively with channelrhodopsin-2 (ChR2). This enabled us to reliably identify CA neurons during unit recording sessions using optogenetic activation. Neurons were classified as CA if they consistently fired spikes time-locked to 5-ms blue light pulses. We recorded activity of these optogenetically identified CA neurons during exploration of environments with familiar and novel floor substrates.

Results & Conclusion: We found that CA neurons in VTA and LC selectively increase their firing rate in novel environments, relative to both a familiar environment and a home cage baseline. Our results implicate both of these nuclei as potential sources of hippocampal dopamine released during novelty exploration, and set the stage for optogenetic activation of these neurons during behavioural studies of memory persistence.

Supported by European Research Council and Medical Research Council.

Poster Ref: P1-D-007

Theme: D: Learning, Memory and Cognition

Catecholaminergic control of initial memory consolidation in mice.

Tomonori Takeuchi[1], Adrian Duszkiewicz[1], Dorothy Tse[1], Patrick Spooner[1], Karl Deisseroth[2] and Richard Morris[1]

[1]Centre for Cognitive and Neural Systems, University of Edinburgh, [2]Department of Bioengineering, Stanford University

Rationale: The synaptic tagging-and-capture theory of initial memory consolidation holds that memory persistence can be altered by prior or subsequent patterns of neural activity. Our laboratory has developed a realistic everyday appetitive paradigm for mice confirming that unrelated novel experiences can facilitate the persistence of spatial memory (Takeuchi *et al.*, BNA 2013 abstract). We have now expanded our analysis to include pharmacology and optogenetics with aim of identifying the specific neuromodulatory systems that mediate this effect. An influential model of initial memory consolidation points to the critical role of catecholaminergic (CA) neurons in the ventral tegmental area (VTA) (Lisman *et al.*, TINS, 2011), but recent evidence also implicates locus coeruleus (LC) as a potential source of dopamine in the hippocampus (Smith and Greene, J. Neurosci., 2012).

Methods and Results: In Study 1, tyrosine hydroxylase-Cre knock-in (Th-Cre) mice learned the win-stay rule of selectively finding the varying location in an 'event arena' where food is available on that day. Persistence of this transient spatial memory, tested 24h later, could be enhanced by 5-min exploration of an open field with a novel floor substrate 30 min after encoding. A series of further tests established that pharmacological blockade of dopamine D1/D5 receptors but not beta-adrenergic receptors in hippocampus during novelty exploration prevented novelty-induced enhancement of memory persistence.

In Study 2, another cohort of Th-Cre mice, in which channelrhodopsin-2 (ChR2) was expressed in CA neurons of both VTA and LC using a Cre-dependent adeno-associated virus, was then trained on the same 'event arena' task. The critical tests of this study involved substituting novelty with optogenetic activation of CA neurons in either VTA or LC at 30 min after memory encoding. ChR2-mediated photoactivation of CA neurons in either VTA or LC enhanced persistence of spatial memory in a manner that mimics the effect of novelty.

Next steps: We are now using pharmacology to explore whether the effect of optogenetic photoactivation of CA neurons in VTA and LC on memory persistence is dependent on activation of D1/D5 receptors in the hippocampus.

Supported by European Research Council.

Poster Ref: P1-D-008

Theme: D: Learning, Memory and Cognition

Differences in retrieval induced gene expression of memory traces consolidated during sleep or novelty.

Justin Jacobse, Lisa Genzel, Janine Rossato and Richard Morris

CCNS, University of Edinburgh

Background: For memory traces to be successfully recalled, they need to be consolidated. Different factors thought to influence this process are (1) novelty exposure that enhances the persistence of a hippocampal trace *via* neuromodulation; and (2) sleep that aids systems consolidation and thus a cortically based memory. To determine if sleep leads to retrieval of a cortical and novelty to a hippocampal memory trace, rats were trained in a watermaze followed by sleep or novelty+sleep deprivation. Subsequently at a 7d retrieval, expression levels of immediate early genes thought to represent activity or plasticity were assessed in medial prefrontal cortex and hippocampus.

Methods: Rats learned an escape platform location in a watermaze, followed by a 6h period of sleep or novelty+sleep deprivation. After 7d the rats had a probe trial without any platform present after which the rats were culled and their brains dissected for a real-time qPCR analysis of medial prefrontal cortex and hippocampus. c-Fos, Arc, and Zif268, normalized to 18s and home cage controls, were measured.

Results: In this between subject design zone analysis showed no group differences in 7d probe trial allowing for direct comparison of qPCR data. Further, movement analysis confirmed that rats with the sleep condition had a normal sleep pattern. Pairwise analysis of rats with sleep in their consolidation window compared to novelty+sleep deprivation revealed an interaction between brain area and gene for gene expression level. Expression of activity gene c-Fos was found to be lower in medial prefrontal cortex than in hippocampus, whereas expression of plasticity genes Arc and Zif268 showed a reversed effect. Analysis normalized to homecage controls showed higher expression of all genes in hippocampus versus medial prefrontal cortex.

Conclusion: Retrieval of memory consolidated during sleep showed increased plasticity indicating network updating, and decreased activity pointing to easier access to those traces, for medial prefrontal cortex compared to hippocampus. The opposite pattern was seen for novelty. These data therefore suggest that memory traces are consolidated to medial prefrontal cortex during sleep. In contrast, retrieval of a novelty memory trace induced plasticity in the hippocampus.

Poster Ref: P1-D-009

Theme: D: Learning, Memory and Cognition

Outcome expectations influence the amplitude of the feedback-related negativity in patients with major depression.

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Introduction: Recent work has suggested that neural sensitivity to rewards using feedback-related negativity (FRN), a relatively negative deflection in the event-related potential (ERP) 230–330 ms after the delivery of a probabilistic reward, may be a biomarker for studying reward sensitivity in depression. Previous studies have showed a reduced FRN response in depression. However, it is unclear if the observed FRN activity is related to the representation of expectancy and clinical anhedonic symptoms. This study investigated whether expectations about outcomes have an impact on the FRN and the link between the FRN and hedonic capacity in patients with major depression.

Method: Twenty-one patients with major depression and 25 healthy individuals were investigated. This study used a simple reward task in which on each trial the stimulus cue predicted the outcome with 80% probability. ERPs elicited by the outcome which was consistent (expected) or inconsistent (unexpected) with the predictions were examined. Self-reported scales were used to evaluate hedonic capacity and other emotional information.

Result: This study found that patients with depression had reduced FRN, calculated as the difference between monetary losses and gains, when the former cues can consistently predict the latter outcomes. Furthermore, the healthy individuals displayed increased FRN response when the outcome was consistent with prediction compared to those conditions where the outcome was inconsistent with prediction; however, the patients with depression displayed a reverse trend, indicating a blunted neural response to reward (see Figure 1). In addition, the unexpected difference wave amplitude and the mean amplitude on unexpected reward trials were associated with anhedonic symptoms in patients with depression.

Conclusion: These finding indicated that feedback-related negativity in major depression patients was sensitive to the valence of cues (reward or no-reward) and the expectancy to feedback (expected or unexpected). In addition, the relationship of anhedonic symptoms and the neural response of reward in depression patients also supported that opinion that FRN may be a useful measure of abnormalities of reward sensitivity in depression.

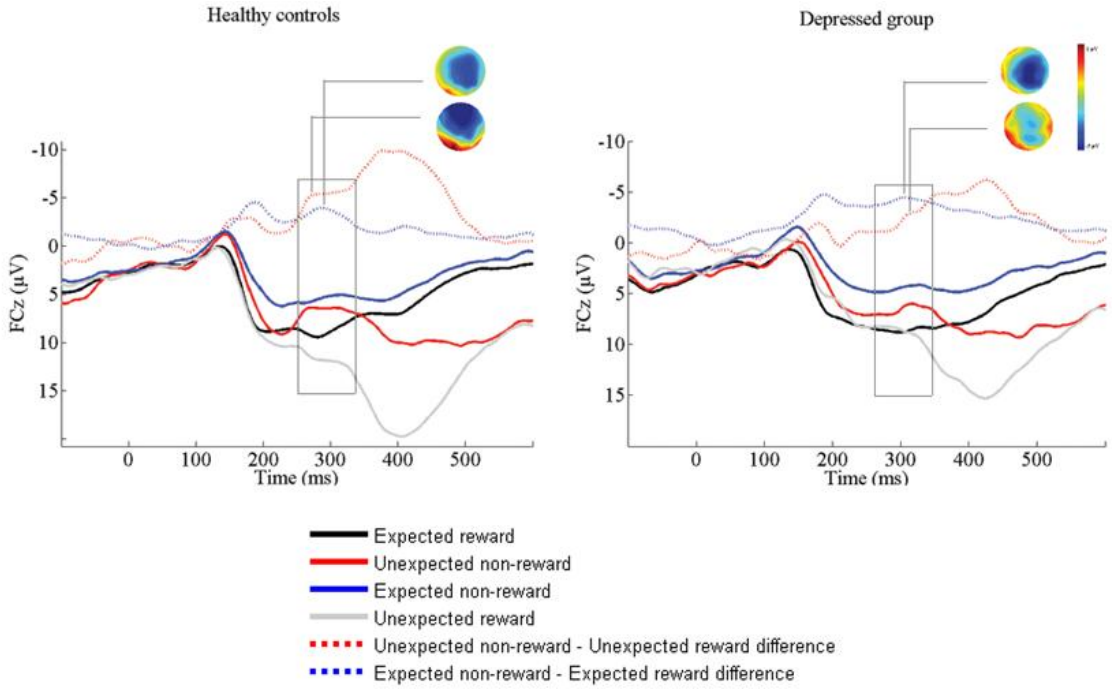


Figure 1 Feedback-locked ERP averages which elicited by the cues and the Expected and Unexpected difference waves for the two groups at FCz.

Poster Ref: P1-D-010

Theme: D: Learning, Memory and Cognition

Probiotics: can good bacteria aid object recognition?

Sumit Mistry, Laura Stockwell, Caroline O'Hagan and Mark Good

Cardiff University

Psychiatric illnesses such as depression are often found associated with gastrointestinal problems such as IBS. Numerous studies show gut micro flora play a pivotal role in the health of the host, with evidence suggesting probiotics and antidepressants are able to improve both the IBS and depression. Currently, there is no conclusive work examining the effect of probiotics in both humans and rodents when examining a barrage of cognitive tests. Object recognition tasks assess a network of brain areas including the perirhinal, hippocampal and medial prefrontal cortices. The brain gut axis (BGA) allows bidirectional communication suggesting altering levels of probiotics in the gut would impact on brain function. Desbonnet *et al.*, (2010) revealed probiotic and citalopram administration induced changes in neurotransmitter precursor levels, particularly serotonin. This study had two aims, of which the first was to determine whether probiotic supplements could affect object recognition memory in Lister Hooded rats. Secondly, to observe the effect of i.p. injection of citalopram hydrobromide on the object novelty paradigm. The data revealed probiotic administration significantly enhanced object novelty and object in place tasks with 1 hour and 5 minute delays respectively suggesting alterations in perirhinal and hippocampal networks. In contrast, a significant deficit in the citalopram injected animals at 1 hour was seen, suggesting that with this probiotic, there is no apparent parallel. Interestingly, further work has shown significant alterations in levels of GABA in the frontal cortex, providing additional evidence of the BGA and its bidirectional communication.

Poster Ref: P1-D-011

Theme: D: Learning, Memory and Cognition

The impact of threat of shock induced stress on cognition: a test-retest reliability study.

Jessica Aylward, Jonathan Roiser and Oliver Robinson

Institute of Cognitive Neuroscience, UCL

It is increasingly recognised that current diagnostic categories, based upon subjective self report of symptoms, do not adequately capture the underlying mechanistic abnormalities in mood and anxiety disorders. By way of example, the majority of individuals who meet criteria for these diagnoses fail to respond to the recommended first line treatments. As such, there is a recent push towards more a neurobiologically informed approach to psychiatric diagnosis encompassing, for instance, physiological, cognitive and neuroimaging approaches. Nevertheless, the success of these approaches is often judged according to current best-clinical-practice self-report based diagnoses. If we accept that current diagnoses are inadequate then this circular approach will ultimately fail to identify superior diagnostic approaches. In this study we take a different approach. Stress has long been thought to be a precipitating factor in mood and anxiety disorders, with some individuals particularly vulnerable to stress. Threat of unpredictable shock is a translational, within-subject, stress induction that can induce neurobiological states associated with pathological anxiety (Robinson *et al.* 2012, 2013, 2014). Classical diagnoses rely on asking an individual how they react to stress; in this study we attempt to quantify this in a non-subjective fashion by exploring the impact (on reaction time/accuracy) of experimentally-induced stress on simple neurocognitive tasks that have been previously shown to be sensitive to threat of shock. The stability of these stress-induced changes was assessed in a wide-ranging healthy sample on two separate testing sessions separated by at least two weeks. This test-retest reliability was compared to 'classical' self-report measures of trait depression and anxiety. Preliminary findings (n=32) suggest that threat-potentiated reaction time ($F=6$, $p=0.02$) in a sustained attention task is reliable across sessions ($r=0.5$, $p=0.004$) whilst also moderately tracking self-reported depression symptoms ($r=-0.4$, $p=0.04$). The ultimate goal of this work is to develop a non-subjective and stable trait measure of stress-responding that we can use as an index of mood and anxiety disorder vulnerability to assess new approaches to mood and anxiety disorder treatment and diagnosis.

Poster Ref: P1-D-012

Theme: D: Learning, Memory and Cognition

Processing time and space: mammillothalamic lesions disrupt recency memory judgments.

Andrew Nelson and Seralynne Vann

Cardiff University

There is good evidence that mammillary body damage causes robust spatial learning deficits in rodents, but the importance of this structure for non-spatial memory has received less attention. Rats with mammillothalamic lesions were tested on tests of recency judgements as well as recognition memory. To measure recency memory, rats were allowed to explore multiple familiar objects, some of which had been explored more recently. In one condition (between-block recency), rats were presented with two lists of objects separated by a delay, thereby creating two distinct blocks of stimuli. In the second condition (within-block recency), rats were presented with a continuous list of objects and, after a delay, were required to distinguish between items encountered early and late in the same list. Mammillothalamic lesions severely disrupted performance on both tests of recency memory but also appeared to impair recognition memory. However, when required to discriminate between just two objects on the basis of either recency or familiarity, the mammillothalamic tract lesion animals performed at comparable levels to control animals. These data suggest that the mammillary bodies and their inputs *via* the mammillothalamic tract to the anterior thalamus support recognition and recency memory by reducing proactive interference.

Poster Ref: P1-D-013

Theme: D: Learning, Memory and Cognition

Medial prefrontal cortex is not required for, but can modulate, hippocampus-dependent behaviour based on rapid learning of changing goal locations on the watermaze delayed-matching-to-place test.

Stephanie McGarrity, Sorley Somerled, Curtis Eaton, Rob Mason, Marie Pezze and Tobias Bast

University of Nottingham

Many everyday situations involve behaviour based on rapid learning of changing goal locations (*e.g.*, a parking space) in a familiar environment. A rodent model is the watermaze delayed-matching-to-place task, requiring navigation to a daily-changing escape location. This task depends critically on the intermediate hippocampus, which combines substrates of rapid accurate place encoding with strong links to behavioural-control sites, including medial prefrontal cortex (mPFC) (Bast *et al.*, 2009, PLoS Biol). The mPFC has been implicated in planning and decision making on hippocampus-dependent tasks (Miller & Cohen, 2001, Ann Rev Neurosci; Euston *et al.*, 2012, Neuron). Here, we examined the role of the mPFC in watermaze delayed-matching-to-place performance, using functional inhibition of this region by muscimol microinfusion and disinhibition by picrotoxin, both of which we have shown to markedly affect prefrontal neural and behavioural function (Pezze *et al.*, 2014, J Neurosci).

We first showed that functional inhibition of the intermediate hippocampus by muscimol markedly disrupted watermaze delayed-matching-to-place performance, confirming this region's key role. *In vivo* electrophysiological experiments indicated that functional inhibition mainly reduced hippocampal burst firing. Functional inhibition of the mPFC did not affect watermaze delayed-matching-to-place performance. Functional disinhibition of the mPFC by picrotoxin left search preference for the correct location largely intact, but biased rats' behaviour towards focused search.

These findings corroborate that the intermediate hippocampus is critical for behaviour based on rapidly updated goal-location memory, as tested on the watermaze delayed-matching-to-place task. In contrast, mPFC activity is not required, as shown by intact task performance following prefrontal functional inhibition. However, mPFC activity may modulate such hippocampus-dependent behaviour, as shown by the increased bias towards focused searching following prefrontal neural disinhibition. In view of these findings, subcortical behavioural-control sites with strong links to intermediate hippocampus, including ventral striatum, may play an important role (Bast, 2011, Curr Opin Neurobiol).

Poster Ref: P1-D-014

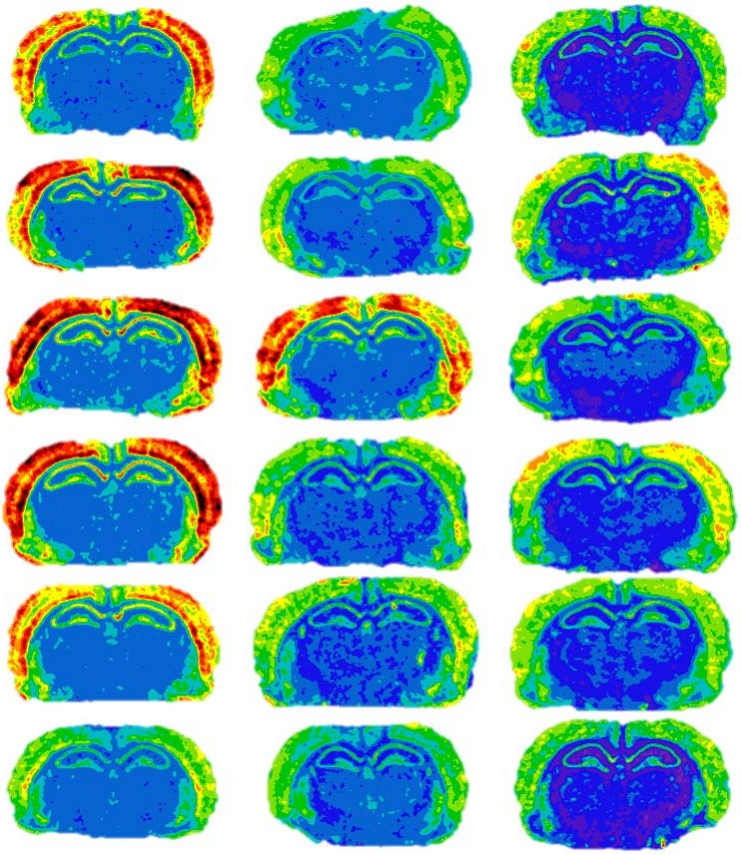
Theme: D: Learning, Memory and Cognition

Postsynaptic density short Homer proteins in associative learning.

Nicholas Clifton, Kerrie Thomas and Jeremy Hall

Cardiff University

Proteins within the postsynaptic density (PSD) are involved in mediating the intracellular signalling cascades that lead to synaptic plasticity. Alterations in PSD proteins could underpin abnormal synaptic plasticity demonstrated in neuropsychiatric disorders such as schizophrenia. Since PSD Homer1 proteins are involved in the restructuring of the PSD following neuronal stimulation, we evaluated their potential involvement in memory consolidation following contextual fear conditioning, using *in situ* hybridization and immunoblotting. Fear-conditioned adult rats displayed a transient increase in Homer1a and Ania-3 expression in CA1, CA3 and dentate gyrus regions of the hippocampus. The change in Homer1a mRNA was maintained from 30 min post-conditioning until at least 4 h post-conditioning. Conversely, the increase in Ania-3 expression was more short-lived, peaking 30 min post-conditioning and returning to baseline by 2h. This is the first time that a differential time course of expression for the two Homer1 activity-induced isoforms has been demonstrated. Homer1a was similarly induced solely from exposure to the novel context, 2h post-exposure. Interestingly, following the recall or extinction of fear memory, a similar differential pattern of expression of the two isoforms was observed. These results suggest distinct roles for Homer1a and Ania-3 in memory consolidation and support their involvement in synaptic plasticity mechanisms relevant to psychiatric disease.



Expression of Homer protein isoforms following contextual fear conditioning. Each isoform differs in their time course of expression. mRNA quantified using *in situ* hybridization.

Poster Ref: P1-D-015

Theme: D: Learning, Memory and Cognition

A role for rodent adult neurogenesis in the adaptation to an unpredictable, threatening environment.

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New neurons are born in the dentate gyrus throughout life. Previous work in our lab showed that new neurons diminish behavioural responses to stress. It is unclear precisely how they do this and what contribution they make towards emotionality. One possibility is that these neurons affect the appraisal process or alter the perception towards an uncertain threat. We used mice that express the HSV-tk transgene (TK) under a GFAP promoter to selectively ablate adult-born neurons and to investigate responses to unpredictable, aversive experiences. In a fear conditioning task, a tone or light that always predicted an upcoming shock ('reliable conditioning') produced similar freezing and startle behaviours in TK and wild type (WT) littermate controls. However, when additional cues were added so that only 50% of cues predicted shocks ('ambiguous conditioning'), TKs froze and startled less than WT mice. This same pattern of results was reflected in neural activation of the mature granule cells and CA3 pyramidal cells as measured by c-fos activation; TKs trained in the ambiguous condition showed decreased activation relative to WTs and all mice in the reliable condition. Interestingly, cued fear conditioning has traditionally been seen as a hippocampus-independent task, but these findings show that the hippocampus is engaged when ambiguity about the cue is introduced. To look for lasting consequences of an unpredictable, aversive experience, mice were tested in the novelty-suppressed feeding task following reliable or ambiguous fear conditioning. Following ambiguous conditioning, WTs showed greater latency to eat food in a novel environment, while reliable conditioning had no effect on these mice. TKs, however, showed intermediate increases in latency regardless of the type of conditioning. Clamping stress hormones at low levels prevented the increased latency in WTs after ambiguous conditioning but had no effect on TKs. These findings suggest that new neurons enhance protective stress-related behaviours in response to unpredictable threat and also regulate responses to future novel situations in a glucocorticoid-dependent manner. These changes could bias behaviour to optimally adapt to adverse environments.

Poster Ref: P1-D-016

Theme: D: Learning, Memory and Cognition

Visuospatial boostrapping in older adults and MCI.

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Background: Recent studies on verbal immediate serial recall (Darling *et al.*, 2010; 2012; 2013; 2014) show evidence of the integration of information from verbal and visuospatial short term memory with long term memory representations. This so-called 'visuospatial bootstrapping' (VSB) pattern, in which verbal serial recall is improved when the information is arranged in a familiar spatially distributed pattern, such as a telephone keypad, is consistent with the existence within working memory (WM) of an episodic buffer (EB; Baddeley, 2000).

Objective: The study investigated how visuospatial systems support verbal WM using the visuospatial bootstrapping paradigm, specifically aiming to see if the bootstrapping pattern persisted in a sample of older adults and patients with Mild Cognitive Impairments (MCI).

Materials and Methods: This study included 15 people with MCI (10 females; median age: 68.53 years, SD = 6.18, range 60-80; median years education: 9,6, SD = 5.09) and 26 healthy controls (20 females; median age 67.11 years, SD = 6.55, range 60-77; median years education: 10.85, SD = 4.34). Each participant was assessed with a background neuropsychological battery of tests and an assessment of bootstrapping. The latter tasks compared immediate serial recall performance across two visual display conditions: single digit presentations and standard (familiar) keypad arrays without suggestion as to what memory strategy to use.

Results and Conclusion: The bootstrapping effect was investigated for the first time in a group of MCI patients. The main conclusion is that the bootstrapping effect was present in both in MCI patients and older adults. No difference was observed in the bootstrapping pattern as a consequence of cognitive difficulties in general and the beneficial impact of additional visual information was comparable for MCI and older participants. These data have implications for the understanding of human memory and possibly with future development of rehabilitation strategies for participants with memory impairment. Further data are needed to provide additional evidence.

Poster Ref: P1-D-017

Theme: D: Learning, Memory and Cognition

Spatial orientation in MCI patients and normal elderly.

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Background: Spatial orientation seems to be particularly in detecting early cognitive impairments. An effective method to investigate the mechanisms which allow for the development and maintenance of spatial awareness is the comparison between different environments. One possible explanation about how implicit information can drive people into memory tasks comes from studies on priming which appears to be preserved in amnesic patients.

Objective: Investigate whether the mechanisms of priming can reduce errors in two different types of spatial task in a group of normal elderly and subjects with mild cognitive impairment (MCI)

Materials and Methods: 45 patients entered the study: N = 31 normal adults, N = 14 MCI (mean age: 73,6, SD = 5,9, range: 65 to 84; 33 women). Both groups were randomly allocated to one of the conditions, receiving or not the priming. A neuropsychological battery of tests was administered with two tasks for navigation in virtual environments: bird-eye view (Flag and Frame) and egocentric view (Paradigm shift).

Results: It can be observed a significant effect of priming ($F(1, 41) = 6.55$, $p < 0.05$, partial eta square = 0.14). The group with a comparison between environments shows a better performance than the other. The effect of the Task is significant ($F(1, 41) = 10{:}41$, $p < 0.01$, partial eta square = 0:20). The task of egocentric view is easier in comparison with the bird-eye view. In the group of normal elderly priming improves the performance when the environment is bird-eye view. In contrast, MCI subjects show the positive effects only in the egocentric view task.

Conclusions: Our results confirm that conceptual priming is based on the comparison between rooms of different shape reduce errors and increase the spatial awareness, compared to a similar condition in which this comparison is not possible.

Poster Ref: P1-D-018

Theme: D: Learning, Memory and Cognition

Investigating onset of cognitive and behavioural deficits in the rTg4510 mouse model of human tauopathy.

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Eli Lilly, Windlesham

Alzheimer's disease (AD) is a complex multi-factorial disease associated with progressive cognitive and behavioural decline from pre-clinical stages to full dementia. Current treatments are largely palliative, providing only transient symptomatic improvement. In contrast, recently developed disease-modifying agents offer the promise of preventing or slowing decline. Together with the need for early clinical diagnosis, preclinical *in vivo* models capable of appropriately mimicking disease progression are important for the development of such agents.

We present here our efforts to track behavioural decline in the rTg4510 mouse model of tau-associated neurodegeneration. Tau-related changes were investigated in separate cohorts, at two distinct time-points (5 and 12 months), using a battery of behavioural assays followed by post-mortem pathological assessments.

Compared to wild-type (WT) littermates, 12-month old male rTg4510 mice displayed severe behavioural alterations including increased locomotor hyperactivity, decreased spatial reference memory in an aversively-motivated Y-maze and impaired spatial working memory in an appetitively-motivated and automated T-maze. Less profound behavioural deficits were observed in 5-month old rTg4510 animals. These mice exhibited normal locomotor activity and mild-to-moderate deficits in both Y- and T-maze tasks.

Future research will focus on the identification of core pathological substrates for these behavioural deficits and then attempt to prevent or slow these progressive tau-related changes *via* the inactivation of tau expression using doxycycline treatment.

Poster Ref: P1-D-019

Theme: D: Learning, Memory and Cognition

What are the functional consequences of c-fos and zif268 down-regulation in the rat retrosplenial cortex?

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The medial diencephalon (e.g., anterior thalamic nuclei, mammillary bodies and mammillothalamic tract) and hippocampus are important for episodic memory in humans and spatial memory in rats. Lesions to these structures also result in a striking reduction of immediate-early gene expression (c-fos and zif268) in the retrosplenial cortex. Given that the retrosplenial cortex also contributes to memory it is possible that this dysregulation of immediate-early gene expression exacerbates the memory impairments seen following lesions to the medial diencephalon or hippocampus. In order to test this possibility we used an object-in-place task, which is sensitive to mammillothalamic tract, hippocampus and retrosplenial cortex lesions, and used a 3 hour delay between the sample and test phase. To test the suitability of this task for assessing temporary retrosplenial disruption, we first investigated the effects of infusing muscimol into the retrosplenial cortex. Rats were significantly worse on the task when infused with muscimol compared to control infusions; indeed, the muscimol infusions resulted in chance performance as the rats were no longer able to discriminate the displaced objects. To determine whether the down-regulation of c-fos and zif268 is sufficient to affect performance on this task, a second cohort of rats will be implanted with cannuale in the retrosplenial cortex and infused with antisense oligodeoxynucleotides targeting the transcripts of these two genes and able to block their protein expression. The results will help explain the functional implications of the retrosplenial dysfunction found following distal lesions as well as the contribution of these immediate early genes to memory consolidation.

Poster Ref: P1-D-020

Theme: D: Learning, Memory and Cognition

The effects of the three APOE alleles on the default mode network vary with age.

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Introduction: The APOE gene has three alleles (ε2, ε3, ε4) that differentially influence cognitive health. APOE ε4 is the best-established genetic risk factor for late-onset Alzheimer's disease (AD), whereas the ε2 allele may confer protection to AD. Several studies have shown that the effects of ε4 on brain function vary with age. However, little is known about the equivalent for APOE ε2. Here, we sought to discover whether risk and protection for AD were differently represented within the resting brain across the lifespan. In particular, we were interested in a resting-state network called the default mode network (DMN), which is impaired in AD and has gained attention as a potential marker of neurodegenerative processes.

Methods: Fifty-three young (mean age: 24.04 ± 4.92 yrs; 18 ε2/17 ε3/18 ε4), 84 middle-aged (mean age: 45.54 ± 5.09 yrs; 25 ε2/26 ε3/33 ε4) and 163 older healthy individuals (mean age: 69.27 ± 5.21 yrs; 25 ε2/97 ε3/41 ε4) underwent a 3T MRI scan. APOE-related differences were studied using whole-brain voxelwise analyses performed with FSL tools and a standard reference template of resting-state components (2).

Results: Relative to ε3 homozygotes, both the risk group (ε4 carriers) and those with the protective allele (ε2 carriers) had significantly higher functional connectivity in the posterior DMN in young individuals (young: ε2>ε4>ε3). This pattern changed within the old group; old ε4 carriers had the lowest connectivity in the anterior DMN (old: ε2=ε3>ε4). No APOE-related differences in the DMN were observed in the middle-aged group.

Conclusion: Our results are in line with previous studies showing an increased functional connectivity within the DMN in young ε4 carriers (3,4) and a decrease in old ε4 carriers relative to ε3 homozygotes (5-7). We have also made the novel observation that activity within the DMN in ε2 carriers remains relatively stable across the ages. We now aim to develop and use our own template of resting-state components covering the adult lifespan in order to ensure unbiased priors.

References: 1. Filippini *et al.* Neuroimage, 2011. 2. Smith *et al.* PNAS, 2009. 3. Filippini *et al.* PNAS, 2009. 4. Dennis *et al.* Alzheimers Dement, 2010. 5. Sheline *et al.* J.Neurosci, 2010. 6. Machulda *et al.* Arch Neurol 2011. 7. Fleisher *et al.* Neuroimage, 2009.

Poster Ref: P1-D-021

Theme: D: Learning, Memory and Cognition

Executive function and sensorimotor skill in older adults: an intervention study.

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University of Sheffield

Background: The increasing number of elderly people is a societal challenge that is exacerbated by reducing cognitive ability, even in healthy ageing. Traditionally, cognitive impairment was ascribed to loss of frontal lobe function. The recent interest in cerebellar and striatal contributions to cognitive function, allied to the established volume reductions in cerebellum and basal ganglia, and the known impairments in sensorimotor functioning, indicate possible subcortical contributions to the cognitive decline. Recent intervention studies have highlighted the importance of exercise, coordinative as well as aerobic, in increasing both hippocampal and cerebellar volume, with corresponding improvements in both physical and mental performance. The present study investigated further the link between subcortical and cortical function in the elderly by undertaking a coordinative exercise intervention.

Method: 98 healthy older adult volunteers (mean age 68.2, S.D 6.6) participated and were split into control and intervention groups. All participants undertook an initial series of pre-tests designed to evaluate Physical Coordination, Memory, Language Dexterity, Fluid Thinking and Affect, with identical post-tests around two months later. The intervention group undertook an 8 week internet-based coordinative exercise intervention, while the control group continued 'life as normal.'

Results: The intervention group showed significant pre- to post improvements in 12 of the 18 tests, whereas the controls improved significantly on one only. Effect sizes ranged from 0.1 to 0.6. MANOVA revealed significant between-group differences for the physical tasks and for the declarative memory tasks. Individual ANOVAs indicated that the intervention group improved significantly more than the controls on three tests - Balance, Peg Assembly and Delayed Picture Recall.

Conclusions: The results demonstrate the benefits of exercise for the elderly, but to our knowledge this is the first study that has investigated a range of attributes from affective to cognitive to sensorimotor skills. The findings indicate that it is both feasible and beneficial to deliver an internet-based balance and coordination program to older adults, and highlight the opportunities for larger studies.

Poster Ref: P1-D-022

Theme: D: Learning, Memory and Cognition

Real-time oxygen changes in the prefrontal cortex and hippocampal-parahippocampal network during object recognition and displacement tasks.

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During normal exploratory behaviour, rats utilise a complex network of different brain regions to process information about their environment. In object-based tasks, electrophysiological and lesion studies suggest that the perirhinal cortex (PRh) is mainly involved in novelty detection whereas the hippocampus is weighted towards processing spatial information about an object. The perirhinal cortex has a number of reciprocal projections with the medial prefrontal cortex (mPFC) and hippocampal formation, with these regions working in concert to perform functions such as novelty detection and contextual processing. Using constant potential amperometry, it is possible to measure real-time changes in oxygen in the brains of freely moving rats which correlate strongly with changes with BOLD in fMRI. Carbon paste electrodes were implanted into the mPFC, PRh and area CA1 of the hippocampus of male Wistar rats. Following recovery, oxygen measurements were made by applying a potential of –650 mV to the working electrodes and sampling at 1 kHz. A three trial protocol was used with two objects (A and B) presented to rats on the first trial; on the second trial the rats undertook a novel object recognition task (object B from trial one replaced with the novel object C); on the third trial the rats undertook an object displacement task (object C remained in the same place and object A was moved to a novel position, A*). Functional differences in the oxygen signal were found with increases in oxygen in the mPFC and PRh associated with object exploration in all three trials. Larger increases were observed when exploring novel objects compared to familiar. Oxygen changes in CA1 were not associated with object exploration but generalised increases were observed in each of the three trials. In animals that failed to explore any objects, increases in mPFC oxygen levels were observed in response to the presentation of the objects. These data show functional differences between these three brain regions during the object recognition task. This helps understand the interrelationship between the regions during object exploration, especially given the translational power of oxygen sensors as a surrogate for fMRI in awake rats.

Funded by the Irish Research Council (GOIPD/2013/420).

Poster Ref: P1-D-023

Theme: D: Learning, Memory and Cognition

Epigenetic processes and rrole in cognitive function.

Miles Flitton[1], Mariam Muse[1], Donald Warden[2], David Smith[2], Ian Macdonald[1] and Helen Knight[1]

[1]University of Nottingham, [2]University of Oxford

Epigenetic modifications and the mechanisms which underlie their regulation are under increasing scrutiny in research of health and disease states. They are implicated as a biological mechanism of interaction between genetics and environmental influences such as dietary intake, physical exercise, and psychological stressors. One such modification, DNA methylation, has long been associated with the disease aetiology of cancers but more recently investigated in a broad range of neurological and neuropsychiatric phenotypes. The dynamic process of methylation involves recruiting three classes of protein, termed “writers”, “readers”, or “erasers”, with genetic mutations in each class reported to cause familial forms of dementia, developmental delay syndromes, and disparate cognitive phenotypes (Amir, *et al.*, 2005; Boissel, *et al.*, 2009; Klein, *et al.*, 2011). We hypothesise that genetic variation within methylation protein genes underlies changes in methylation patterns and such alterations may consequently influence cognitive function and disease status.

Using longitudinal data from the OPTIMA study collected for individuals with mild cognitive impairment, we report the effect of genetic variation within one of the methylation “writers” on biochemical measures, cognitive performance, and interaction with vitamin B treatment. Subsequent studies will be aimed at direct examination of epialleles as well as interrogating additional cohorts with existing exome sequencing and phenotypic data. This multi-faceted approach will help to provide a fuller picture of the impact of DNA methylation on cognitive function and how such effects may differ across different disease phenotypes and at different developmental time points.

References

Amir, R.E., *et al.* (2005) Mutations in exon 1 of MECP2 are a rare cause of Rett syndrome, J Med Genet, 42.

Boissel, S., *et al.* (2009) Loss-of-Function Mutation in the Dioxygenase-Encoding FTO Gene Causes Severe Growth Retardation and Multiple Malformations, Am J Hum Genet, 85, 106-111.

Klein, C.J., *et al.* (2011) Mutations in DNMT1 cause hereditary sensory neuropathy with dementia and hearing loss, Nat Genet, 43, 595-U140.

Poster Ref: P1-D-024

Theme: D: Learning, Memory and Cognition

Crossmodal motion adaptation in the human brain? An electrophysiological study using visual and auditory free-field motion.

Ramona Grzeschik[1], Jesko L. Verhey[1], Jörg Lewald[2], Michael B. Hoffmann[1] and Stephan Getzmann[3]

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When testing within one modality, adaptation to visual or auditory motion greatly affects the visual or auditory motion-onset evoked potentials (VEPs, AEPs) to the onset of subsequent motion (vision: Hoffmann *et al.*, 2001; audition: Grzeschik *et al.*, 2013). Here, we combined both modalities and tested whether adaptation to visual motion affects the auditory motion-onset response.

VEPs and AEPs of 21 subjects were recorded from 57 EEG channels in six blocks, in which each combination of visual adaptation (leftward motion, rightward motion, spatially scattered motion) and modality of test stimulus (visual or auditory leftward motion) was presented (Fig. 1). In each trial, the 330-ms test motion started after a 1000-ms epoch of a central stationary stimulus. Each block was preceded by a 2-min motion adaptor. Here, 105 motion adaptation stimuli (used also for top-up adaptation during the adaptation phase of the recordings), separated by 500-ms silence intervals, were presented. VEPs and AEPs were analysed for the Same-Direction, Opposite-Direction, and Scatter adaptation conditions (referred to as Ada Same, Ada Opposite, and Scatter).

For the unimodal condition, the motion-onset VEPs indicated a direction-specific effect of adaptation: The change-N1 (cN1; around 150 ms) and change-P2 (cP2; around 250 ms) amplitudes of Ada Same were significantly smaller than that of Ada Opposite. For the crossmodal condition, the motion-onset AEPs showed an effect of motion history by a positivation of change-P1 (cP1; around 100 ms) that was significantly larger for the conditions Ada Same and Ada Opposite than for the Scatter condition. No significant effects were found for cN1 or cP2. In summary, the results clearly confirmed the existence of a direction-specific effect of motion adaptation within the same modality, but suggested a crossmodal effect, in which early processes of auditory motion detection were affected by preceding visual motion independent of motion direction.

References

Hoffmann MB *et al.*, 2001. Directional tuning of human motion adaptation as reflected by the motion VEP. Vision Res 41: 2187-2194.

Grzeschik R *et al.*, 2013. Direction-specific adaptation of motion-onset auditory evoked potentials. Eur J Neurosci 38: 2557-2565.

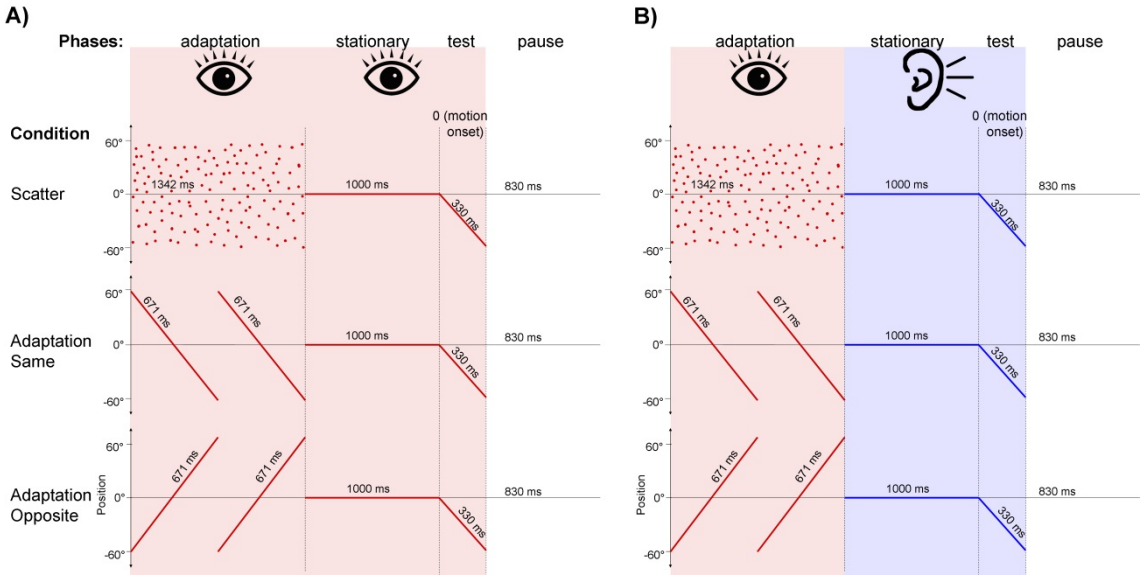

Fig. 1: Time courses of adaptation conditions (stimulus position vs. time). The different stimulation phases were repeated in a cyclic design within each adaptation condition. Visual adaptation was presented prior to (A) visual or (B) auditory stationary and test stimuli.

Poster Ref: P1-D-025

Theme: D: Learning, Memory and Cognition

Head direction and spatial properties of single-units recorded in the anterior retrosplenial cortex of the freely-moving rat.

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The rodent retrosplenial cortex (RSC) is the most caudal subdivision of the cingulate cortex; it is one of the most prominent subdivisions of the rat brain, extending over half the length of the medial surface of the neocortex. It is also ubiquitously present in many higher order mammals including the primates and human. RSC has been implicated in episodic memory, navigation and in planning for the future. In neurophysiological studies, only the spatial and non-spatial properties of the neurons of the posterior RSC have been investigated. The posterior portion of RSC contains many cells which are strongly correlated with head direction (head direction cells); additionally, some of these cells show anticipatory properties as well as location-dependent activity. However, the spatial and temporal properties of the anterior portion of RSC have largely been unexplored, possibly due to technical reasons, including the narrow width of the structure, and the difficulty of targeting anterior RSC with electrodes given the sagittal sinus almost occludes direct, dorsal access. Here, we investigated the spatial and temporal properties of the anterior portion of the RSC by performing recordings of multiple single neurons in the freely-moving rat using 32-channel drivable microelectrode arrays. We found that the anterior RSC contains many head direction cells with differing firing properties to that of the posterior RSC. Cells recorded from the anterior RSC when correlated with angular velocity (speed of head movement), running speed, place (location of rodent in arena) and head direction. The differing firing characteristics of cells in the posterior and anterior RSC could be attributed to the varying synaptic weight of inputs along the anterior-posterior gradient of the RSC by brain structures strongly correlated with spatial memory and cognition such as the hippocampal formation or anterior thalamus.

Poster Ref: P1-D-026

Theme: D: Learning, Memory and Cognition

Functional cognitive disorders: their prevalence and characteristics.

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Introduction: It is normal to sometimes experience minor lapses in memory, attention or problem solving. Some patients have persistent subjective cognitive complaints for which no neurodegenerative cause can be found. There is often underlying psychological distress, and these patients are considered to have a functional (psychological) cognitive disorder. It is important to accurately diagnose these individuals, so they are offered appropriate treatment, and to avoid including them in trials of agents to treat neurodegenerative disease We reviewed cases of functional cognitive disorder registered on the North Bristol Trust Cognitive Neurology and Dementia Clinic database.

Methodology: The cognitive clinic database was searched for patients with a final diagnosis of a functional cognitive disorder. Demographic information, age at symptom onset and referral, underlying precipitants and co-morbid medical or psychiatric conditions were recorded. Ethical approval for this study was given by North Bristol NHS Trust.

Results: 196 patients consented to their data being used for research purposes. 23 patients with a functional cognitive disorder were identified. All were 60 years old or younger, and represented 33.3% of those on the database in this age group. 65% of patients were female. The median age at symptom onset was 47 years, and median duration of symptoms prior to presenting to the cognitive clinic was 1 year. Only 2 patients failed effort testing. 39% performed in the normal range on the Montreal Cognitive Examination. Most patients had clear external stressors and 3 met criteria for post-traumatic stress disorder.

Discussion: This study shows how prevalent functional cognitive disorders are within the cognitive clinic, particularly in younger patients. Surprisingly, most patients past tests of effort, but other aspects of neuropsychological assessments showed inconsistencies and implausible results. Therefore effort testing may not detect those with psychogenic cognitive problems. Patients were often not reassured by normal imaging or blood work-up and over interpreted trivial cognitive lapses. Future work will explore attitudes towards health and cognition in this group, and how support services can be devised to improve their cognitive performance.

Poster Ref: P1-D-027

Theme: D: Learning, Memory and Cognition

Wakeful rest promotes cognitive map accuracy in young and older adults.

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Our ability to flexibly navigate spatial environments is contingent upon accurate mental representations, or cognitive maps, which are formed automatically during environment exploration. Cognitive maps critically depend on hippocampal place cells. In rodents, place cells replay recently travelled routes, especially during periods of behavioural inactivity (sleep/wakeful rest). This neural replay is hypothesised not only to promote the consolidation of the travelled route but also to support the wider consolidation and elaboration of these memories into accurate cognitive maps. In humans, wakeful rest promotes the consolidation of basic verbal material (*e.g.* word lists); however the effects of wakeful rest on the wider consolidation and elaboration of memories are unknown. In the two experiments reported here, we examined whether wakeful rest benefits the formation of new cognitive maps in humans. In Experiment 1, 40 healthy young adults learned a route through a realistic virtual town environment, and then either rested wakefully or engaged in an unrelated perceptual task for 10 minutes. The two groups were equally able to learn the route prior to the delay. However, in an unexpected cognitive map test administered after the delay, the rest group showed enhanced accuracy when estimating directions between distant landmarks. In Experiment 2, we examined whether healthy ageing influenced (i) performance in the cognitive map test and (ii) the benefit of wakeful rest in this test. Twenty healthy young and 20 healthy older adults underwent the same procedure as in Experiment 1. As previously, wakeful rest enhanced the accuracy of responses in healthy young adults. Moreover, while an age-related decline in performance was observed, the benefit of wakeful rest extended to older adults. The degree of the benefit of wakeful rest was unaffected by healthy ageing. We propose that wakeful rest promotes the consolidation of new cognitive maps in young and older adults, possibly *via* superior neural replay.

Poster Ref: P1-D-028

Theme: D: Learning, Memory and Cognition

Parvalbumin interneurons modulate prefrontal theta and gamma rhythms to enable spatial working memory.

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Alterations in the inhibitory circuitry of the pre-frontal cortex (PFC) are thought to underlie some of the cognitive deficits observed in schizophrenia. These alterations particularly concern a subset of GABAergic interneurons that express the calcium-binding protein parvalbumin (PV) as shown in post mortem studies in patients and animal models of the disease. To assess the contribution of PV+ interneurons to PFC-dependent behaviours, we selectively blocked the output from those cells via virus-mediated expression of tetanus toxin light chain (TeLC). We found that functional removal of PV+ neurons causes specific impairments in working memory and cognitive flexibility, which represent key cognitive deficits in schizophrenia. Cognitive events bind ensembles of neurons together to bring about a uniform behavioural response. The elements of these ensembles are typically neurons with their own individual properties encoding/retrieving specific task parameters so that an overall appropriate response pattern can be observed. Yet, the same neurons may exhibit differential neuronal activity in a spatial versus a non-spatial task, or a short-term relative to a long-term memory task. As oscillatory brain activity in the theta (4-9 Hz) and gamma (20-80 Hz) frequency range correlates with working memory performance and patients suffering from schizophrenia show alterations in these frequency bands, we measured local field potential oscillations in the medial PFC and in the hippocampal CA1, a second brain region implicated in working memory. Results confirm a significant decrease in PFC theta and gamma power in the PV-TeLC mice relative to control animals. Interestingly hippocampal activity in the theta and gamma range was also diminished. Further analysis of different stages of the working memory task shows that the PV-TeLC animals are unable to modulate neuronal activity depending on the cognitive demand. These results show that PV+ interneurons in the PFC control task-relevant neuronal activity in different brain regions engaged with working memory. Impaired signalling from PFC PV+ interneurons may thus underlie the neurophysiological alterations and parallel cognitive deficits found in schizophrenia.

Poster Ref: P1-D-029

Theme: D: Learning, Memory and Cognition

Neuronal correlates of value based decision making depend on information gathering strategies.

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Animal and human lesion studies describe a double dissociation between anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC) damage where ACC lesions cause deficits in action based decision making whereas OFC lesions affect stimulus based decision making suggesting that neuronal populations within different parts of prefrontal cortex may represent relevant decision variables in different frames of reference. Such populations may therefore be differently relevant to the decision process depending on how information is gathered.

To study multi-attribute value based decision-making, monkeys were taught a set of picture value associations for each of two attributes (reward probability and size). Subjects were then presented with two pictures (one from each attribute) on each side of a fixation point and made choices between left and right options. Importantly, subjects were free to saccade to the different pictures to gather information about attributes/options before indicating their choice by moving a joystick to the left/right. Eye movements provided a proxy for the information gathering strategies influencing decision-making. Each cue consisted of two important properties other than its value; firstly its position on the screen (left or right) which was tied to the action required to obtain the option. Secondly, the cue can denote either a probability or magnitude attribute.

Single neurons were recorded from ACC, OFC, lateral PFC (LPFC) and ventromedial PFC (vmPFC) while subjects performed the task. At first cue presentation, neurons throughout all four brain areas encoded its value. However, a subpopulation in ACC and LPFC differentially encoded action value. In contrast, a significant subpopulation of OFC neurons was seen to differentially encode cue value depending on attribute type. Analysis of neuronal responses to subsequent cues have found that OFC and ACC maintain this dissociation of value reference frames throughout the trial but value signals evolve from value encoding to encoding the value of what will be eventually chosen. Also, populations of neurons in all regions performed specific computations based on different information gathering strategies suggesting that value computation is intimately linked with information gathering.

Poster Ref: P1-D-030

Theme: D: Learning, Memory and Cognition

Risk-taking, response inhibition and the right inferior frontal gyrus.

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The ability to inhibit motor responses has been linked to risk-taking behaviour, including gambling. This suggests that those with high trait levels of sensation seeking, the major personality determinant of risk taking, may have poorer response inhibition. We provide converging evidence to support this: first by testing whether performance on a stop-signal response inhibition task relates to levels of sensation seeking, and second, by assessing whether variation in sensation seeking is associated with grey matter volumes of a region causally implicated in response inhibition, the right inferior frontal gyrus (rIFG).

For study one, 87 healthy subjects (25 males) completed a measure of sensation seeking together with a stop-signal task. For study two, 152 healthy subjects (45 males) completed the sensation seeking measure and underwent T1-weighted MRI at 3T. We carried out a voxel-based morphometry analysis using DARTEL to examine grey matter volumes, with a region of interest centred on the rIFG.

UPPS Sensation Seeking, but not other impulsivity facets, correlated with Stop-Signal task performance, with higher sensation seeking associated with poorer response inhibition. The DARTEL analysis revealed significant negative associations between sensation seeking and grey matter volumes in the rIFG, but also the right orbitofrontal cortex and right middle temporal gyrus.

We provide converging evidence to support the link between risk taking and motor inhibition, both at a psychological and at a biological level. This may explain why individuals with disinhibitory disorders sharing genetic variation with sensation seeking show poor response inhibition and suggests a key role of the rIFG in self-control.

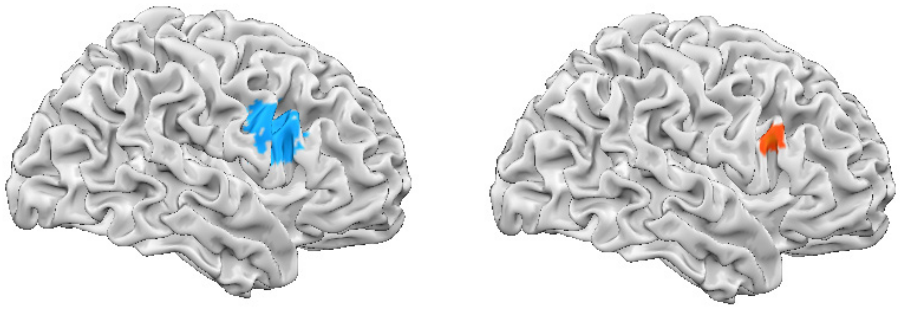

Figure 1. Associations between grey matter volume and trait sensation seeking on the UPPS impulsivity scale were examined within a 10 mm sphere centred in the right inferior frontal gyrus (left), based on a previous study of motor inhibition. The negative association with grey matter volume within the right inferior frontal gyrus can be seen in the right image.

Poster Ref: P1-D-031

Theme: D: Learning, Memory and Cognition

Exploring the effects of disrupting the nucleus reuniens in rats on performance of hippocampus-dependent tasks.

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The nucleus reuniens is thought to be a major route of information flow from the prefrontal cortex to the hippocampus because it is the site of a one synapse connection between the two areas. In addition, lesions or optogenetic inactivation of the nucleus reuniens cause a reduction in trajectory-dependent activity in hippocampal CA1 place cells. Nucleus reuniens lesions might therefore block the prefrontal cortex input to the hippocampus, and thereby deprive CA1 of information about trajectory from the prefrontal cortex. We tested whether the nucleus reuniens is necessary for acquisition and performance of a hippocampus-dependent task in which trajectory-dependent place fields are observed. After lesioning the nucleus reuniens using ibotenic acid, we trained rats on a hippocampus-dependent win-stay, lose-shift task in a double Y maze. The reuniens lesion animals showed no differences in accuracy during acquisition or performance compared to sham operated control rats. This is surprising as it suggests that decreasing trajectory dependent activity in CA1 place cells may not disrupt the ability of animals to learn the task. The double Y maze task could be solved either egocentrically or allocentrically, which may allow animals to compensate for any deficits. To test for deficits in allocentric navigation, we trained animals on a reference memory task in a water maze followed by a reversal of the platform location. Animals in the lesion group showed a significant initial impairment in learning the allocentric task but their performance was comparable to that of the control group after 3 days and there were no differences between groups during reversal of the target location. Conversely, lesion animals learned an egocentric task on the plus maze faster than controls. Our findings are consistent with a role for the nucleus reuniens in the selection or performance of an allocentric navigation strategy, but suggest that it is not required for applying this strategy when the platform location is moved. Moreover, they suggest that any effects of nucleus reuniens lesions on the trajectory-dependent activity of place cells do not lead to impairments in a hippocampus-dependent win-stay, lose-shift task in which trajectory dependent activity is normally observed.

Poster Ref: P1-D-032

Theme: D: Learning, Memory and Cognition

Dopamine D1 receptor stimulation modulates the formation and retrieval of novel object recognition memory: role of the prelimbic cortex.

Marie Pezze, Hayley Marshall , Kevin Fone and Helen Cassaday

Nottingham University

Previous studies have shown that dopamine D1 receptor antagonists impair novel object recognition memory but the effects of dopamine D1 receptor stimulation remain to be determined in the rat. This study investigated the effects of the selective dopamine D1 receptor agonist SKF81297 on acquisition and retrieval in the novel object recognition task in male Wistar rats.

SKF81297 (0.4 and 0.8mg/kg s.c.) given before the sampling phase impaired novel object recognition evaluated 10 min or 24h later. The same treatment also reduced novel object recognition memory when given immediately before the test session. These data indicate that D1 receptor stimulation modulates both the encoding and retrieval of object recognition memory.

Microinfusion of SKF81297 (0.025 µg or 0.05 µg/side) into the prelimbic sub-region of the medial prefrontal cortex (mPFC) before the sampling phase also impaired novel object recognition memory, suggesting that the mPFC is one important site mediating the effects of D1 receptor stimulation on visual recognition memory.

Poster Ref: P1-D-033

Theme: D: Learning, Memory and Cognition

Emotional connections need structural connections: interindividual variation in uncinate fasciculus microstructure is related to cognitive empathy.

Bethany Coad, Nils Muhlert, Carl Hodgetts, Mark Postans, Kim Graham and Andrew Lawrence

Cardiff University Brain Research Imaging Center (CUBRIC)

Understanding the thoughts and emotions of others (cognitive empathy) is critical for social interaction and is underpinned by a widely distributed network of fronto-temporal brain regions. The dispersal of these regions implies that the efficiency of their interconnections may impact upon social-emotional functioning. The uncinate fasciculus (UF) is a long-range association fibre tract connecting regions in the frontal and temporal lobes, and is thought to be important for social cognition. Few studies, however, have directly investigated the microstructural properties of the UF in relation to social-emotional functioning in healthy adults. This study addressed this gap by studying the relationship between microstructural characteristics of the UF and performance on the Mind in the Eyes task (MITE), a measure of cognitive empathy; this was contrasted with a control odd-one-out ("oddity") task of facial identity processing. Diffusion-weighted MRI and behavioural data were collected from 41 healthy participants. Diffusion-MRI measures of white-matter microstructure (fractional anisotropy (FA)) were extracted from the left and right UF of each participant, which had been reconstructed using deterministic tractography. FA of the right, but not the left, UF was significantly correlated with performance on the MITE task, but not the face oddity task. These findings extend previous reports of social impairments following UF damage, revealing that this white matter tract is important for cognitive empathy, independent of face perception abilities. The findings highlight the importance of white matter microstructure for understanding interindividual variability in social-emotional processing.

Poster Ref: P1-D-034

Theme: D: Learning, Memory and Cognition

From sound to meaning: neural dynamics of lexical access to conceptual representations.

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How do we access meaning through speech? Understanding the meaning of a concept (*e.g.* camel) requires co-activation of concept's features within a distributed semantic system. Evidence from vision indicates that conceptual information about objects is hierarchically coded along the ventral stream where the representations are built over time by incorporating a concept's semantic (*e.g.* has four legs) and perceptual features (e.g. has beige fur) (Clarke *et al.*, 2013). In the case of spoken words candidate lexical representations are activated in parallel as the speech accumulates. Parallel activation of candidates creates transient competition until the point in the spoken word where the word is uniquely identified (uniqueness point, UP; Marslen-Wilson, 1987). While access to conceptual features through vision is well established it remains unclear how form-based representations activated by speech evolve into semantic representations following phonological and semantic competition.

The present electro-magnetoencephalography (E/MEG) study aims 1) to identify the dynamics with which auditory representations evolve into conceptual representations over time through phonological and semantic competition 2) to define the spatiotemporal dynamics underpinning processing of conceptual feature statistics through speech which we assume to be inherent in natural language processing. Participants performed a lexical decision task with single spoken words of 296 objects. The data was analyzed with a multivariate pattern analysis, spatiotemporal searchlight representational similarity analysis (ssRSA; Su *et al.*, 2012) allowing us to relate specific oscillatory signatures to feature statistics.

The ssRSA revealed early LIFG activity for phonological and semantic competition before the UP. Following the UP we found rapid and recurrent access to conceptual features. Feature activation was marked by activity in a distributed network consisted of bilateral SMG, AG and MTG. Results show that when conceptual representations are accessed through spoken words, concepts that match the auditory input will initially be partially activated. As soon as the pool of candidate concepts is narrowed down to a single concept, the conceptual features of that concept alone are rapidly accessed.

Poster Ref: P1-D-035

Theme: D: Learning, Memory and Cognition

Sex differences in learned fear inhibition are linked to altered gamma oscillations in prefrontal cortex.

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Anxiety disorders like post-traumatic stress are characterized by impaired learned fear inhibition and prefrontal cortex (PFC) dysfunction. These disorders are up to twice as common in women than in men, yet little is known about sex differences in the neural circuitry underlying learned fear inhibition. In rats, the prelimbic (PL) and infralimbic (IL) subregions of PFC play important roles in learned fear expression and fear extinction, respectively. We have recently shown enhanced learned fear expression and persistent prelimbic (PL) cortex activation in females [Fenton *et al.* (2014) Learn Mem 21:55-60]. We used *in vivo* electrophysiology to record theta oscillations (4-12 Hz) in PL and IL during auditory fear conditioning, extinction, and extinction recall in male and female rats. We found that females showed more fear during extinction and its recall, compared to males. This was accompanied by persistent PL theta throughout extinction and extinction recall, whereas PL theta decreased during extinction and its recall in males. In contrast, theta in the infralimbic (IL) cortex increased during extinction and its recall in both males and females. Emerging evidence indicates that PFC gamma oscillations are also involved in learned fear inhibition. Here we re-examined those data to determine if sex differences in learned fear expression and extinction are accompanied by altered gamma activity (30-45 Hz) in PFC. We found that PL gamma decreased during extinction and its recall in males, whereas in females this decrease did not occur. This suggests that persistent PL gamma activation may also be linked to enhanced learned fear expression. We found no change in IL gamma in males or females during extinction, in contrast to theta. Males did show increased IL gamma during extinction recall, suggesting that gamma activity in IL might be preferentially involved in extinction memory processing rather than extinction learning. Importantly, females showed no change in IL gamma during extinction recall, raising the possibility that resistance to extinction is associated with a failure of gamma activation in IL. Taken together, these results indicate that altered gamma and theta oscillations in PFC contribute to sex differences in learned fear inhibition.

Poster Ref: P1-D-036

Theme: D: Learning, Memory and Cognition

Resisting false recognition: an ERP study of mnemonic discrimination.

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There is keen interest in what enables rememberers to differentiate true from false memories and which strategies are likely to be the most effective. This study measured electrical brain activity while healthy young adults performed a mnemonic discrimination task, deciding whether color pictures had been studied, were similar to studied pictures (lures), or were new. Between 500 – 800 ms post-stimulus, event-related potentials (ERPs) for correctly recognized studied pictures and falsely recognized lures had a left centroparietal scalp distribution typical of the parietal old/new effect associated with recollection. In the group as a whole this evidence of false recollection was attenuated for false relative to true recognition, but the parietal effects for falsely recognized lures were also larger in individuals who successfully rejected a greater number of lures as “similar”. Given the absence of evidence of recollection of correctly rejected lures, the data are consistent with reliance on recollection to decide that items were studied, and the possibility that this depends on pattern separation processes preventing recollection of most, but not all, lures. The better performers also showed more pronounced right frontal old/new effects between 800 – 1100 ms for correctly rejected as well as falsely recognized similar lures. Together, the findings suggest that effective rejection of lures meant that false recognition occurred when there was more substantial or more specific false recollection, and support a contribution of evaluative post-retrieval processing to accurate recognition.

Poster Ref: P1-D-037

Theme: D: Learning, Memory and Cognition

Mapping activity patterns in the medial temporal lobe for novel object processing and recognition memory following removal of the perirhinal cortex in rats.

Lisa Kinnavane, Eman Amin, Cristian Olarte-Sanchez and John Aggleton

Cardiff University

Recognition memory is the ability to discriminate novel from familiar stimuli. Recency memory is the ability to discriminate objects with differing degrees of familiarity. Expression of immediate-early genes reveals different patterns of integrated neuronal activity across medial temporal lobe sites when rats are engaged in novel object recognition or recency memory tasks. Using structural equation modelling (SEM) on c-fos data generated from animals engaged in these tasks, we have previously demonstrated that novel object recognition recruited the pathway from lateral entorhinal cortex (cortical layer II or III) to hippocampal field CA3 and, thence, to CA1. Familiar stimuli in a recency task recruited the direct pathway from lateral entorhinal cortex (principally layer III) to CA1 (Albasser *et al.*, 2010).

To determine the extent to which these learning–related networks depend on actively performing a discrimination or simply the presence of novel or familiar stimuli a group of rats was presented with a 20 trial novel/familiar object discrimination task. As a comparison, another group received 20 pairs of novel objects. It has been consistently demonstrated that animals with perirhinal cortex lesions perform significantly worse on object recognition tasks than intact animals. Interestingly however, perirhinal lesions to not cause a decrement in the amount of time rats spend exploring novel objects (Albasser *et al.*, 2011). Thus, half of the animals received perirhinal lesions while the other half served as sham surgical controls in order to examine how novel object processing is altered by the loss of the perirhinal cortex.

Applying SEM to the resulting immunohistochemical c-fos data created pathways of correlated regional interactions both in the intact brains and in brains with perirhinal lesions. Our results indicate that the previously derived network models of hippocampal engagement are associated with the presence of novel stimuli rather than active discrimination, and that lesions to the perirhinal cortex lesions do not disrupt this pattern.

Albasser MM, Poirier GL, Aggleton JP. Eur J Neurosci 2010; 31:134–47.

Albasser MM, Amin E, Iordanova MD, Brown MW, Pearce JM, Aggleton JP. Eur J Neurosci 2011; 34:331–42.

Poster Ref: P1-D-038

Theme: D: Learning, Memory and Cognition

Methylphenidate modulates functional connectivity in the working memory network and improves cognitive performance in patients with traumatic brain injury.

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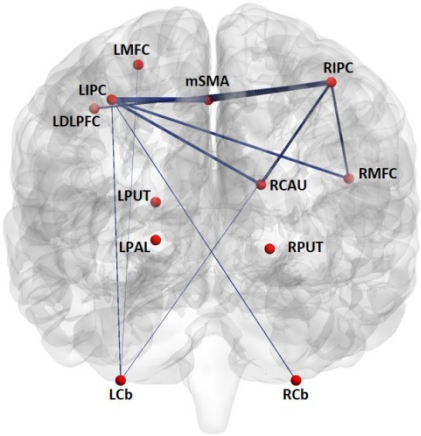
[1]Division of Anaesthesia, Department of Clinical Neuroscience, University of Cambridge, [2]Division of Anaesthesia, University of Cambridge, [3]Department of Psychiatry, University of Cambridge, [4]Barts and the Royal London NHS Trust

Working memory (WM) impairments are common following traumatic brain injury (TBI). Understanding and ameliorating such deficits could substantially improve quality of life for TBI survivors. We investigated functional connectivity (FC) during a WM task in controls and patients to document changes in WM network integration following TBI. FC patterns were compared with behavioural responses in patients in a single-dose, placebo-controlled trial of the cognitive enhancer Methylphenidate to explore functional correlates of possible performance changes.

We acquired fMRI data using the n-back task, from 15 healthy (HC) controls and an age-matched sample of 15 TBI patients. TBI patients were studied on two occasions, one hour after the oral administration of either placebo or 30 mg of Methylphenidate. Behavioural performance was assessed by calculating % Hits and d' for the 2-back condition (a task level that requires both WM maintenance and manipulation). fMRI data were pre-processed and statistically modelled using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/).

Significant differences in behavioural measures for the 2-back task were found between the HCs and TBI Placebo group but not in the comparison between HCs and TBI drug group. We studied connectivity in the network defined by the statistical peaks from the HC activations. The within-network FC analysis revealed that the TBI placebo group had reduced levels of connectivity for nearly three times as many network connections compared to the TBI drug group. When whole brain FC connectivity levels were examined, negative interactions were the most common finding across the three experimental groups. The TBI placebo group demonstrated more widespread and extensive negative interactions during the task than either the TBI drug group or HCs.

Our findings suggest that a) TBI significantly reduces connectivity strength between key areas of the WM network and b) Methylphenidate improves the cognitive outcomes on a WM task. TBI patients given a single dose of Methylphenidate demonstrate patterns of functional connectivity that more closely resemble FC patterns seen in HCs. This result suggests that Methylphenidate may render the WM network in a TBI group more consistent with that of an intact WM network.



Areas of reduced PPI connectivity strength Placebo compared to HCs:

The thickness of the lines represent the degree of significance of the reduction in the correlation between the regions of the WM network for the TBI Placebo condition compared to the HCs. The thinner the lines, the greater the reduction in functional connectivity between these WM regions in the TBI Placebo condition.

Poster Ref: P1-D-039

Theme: D: Learning, Memory and Cognition

Effects of fat bingeing during adolescence on cocaine-induced conditioned place preference in adult mice.

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Unit of Research on Psychobiology of Drug Dependence, Universitat de València, Spain

Adolescence is a developmental stage during which there is synaptic plasticity and vulnerability to different environmental threats, such as inadequate dietary habits or drug abuse. Binge-eating is a specific form of overeating characterized by a dysfunctional appetite marked by intermittent excessive eating. Like drugs of abuse, certain types of food activate common dopaminergic pathways, which is why hedonic eating affects neural mechanisms associated with reward and perpetuates binge-type eating behaviour.

Prolonged exposure to rewarding stimuli like drugs or palatable food can lead to physical dependence, and physical symptoms can appear when the stimulus is removed. The aim of this study was to evaluate the effects of a high-fat diet consumed in a binge pattern and its consequences on cocaine-induced Conditioning Place Preference(CPP). In addition, we assessed the effects of two different high-fat withdrawal states on anxiety levels and extinction of the cocaine-induced CPP.

A total of 60 adolescent male mice of the OF1 strain (21 PND on arrival at the laboratory) were assigned a standard or a high-fat diet and two additional groups were assigned to a high-fat diet with different withdrawal periods. Animals had binge access for 2h, 3 days a week. A significant escalation in consumption of the HFB was observed between the first and last week before CPP, which represented the development of a binge-eating pattern. CPP induced by 6 mg/kg cocaine and anxiety assessed with the Elevated Plus Maze (EPM) took place.

Our results indicate that all groups developed preference for the drug-paired compartment, but this preference was reinstated with a priming dose of 3 mg/kg or 1.5 mg/kg of cocaine only in the groups receiving a high-fat diet in a binge pattern with 15 days of withdrawal. This group also required a significantly longer period for the cocaine preference to be extinguished. The results obtained in the EPM confirmed a higher level of anxiety in the withdrawal groups. We propose that maladaptive behaviour such as binge-eating and its withdrawal are a gateway for the development of addiction, as the withdrawal of dietary fat consumed in a binge pattern substantially increases vulnerability to reinstatement of the conditioned rewarding effects of cocaine.

Poster Ref: P1-D-040

Theme: D: Learning, Memory and Cognition

Neural correlates of emotional response to taste: an EEG study.

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The brain produces a prediction error (PE) in response to a difference between expectation and outcome, an important signal for adaptive learning and optimal decision making. PE signals in EEG are thought to originate in the dopaminergic midbrain and have a source in the anterior cingulate cortex. Previous research utilized monetary reinforcers to compare rewarding and aversive PE, but in this participants only gain money – they are never really 'out-of-pocket'. Here we examined the correlates of personally meaningful aversive PE by using rewarding and aversive tastes. This allowed us to compare positive and negative primary reinforcers from the same modality, something that has not been achieved before.

Twenty participants received rewarding (sweet) and aversive (bitter) tastes, indicated by a cue, while EEG was recorded. Expectations for these tastes were controlled by giving participants cues before taste administration, which indicated the type of taste they would receive and the likelihood of receiving this taste (25% or 75%).

Preliminary analysis on a subsample shows unexpected delivery of sweet and bitter taste produces a stronger positive event-related potential (ERP) than omission of either bitter or sweet taste. This suggests that the ERP differences previously thought to signal reward prediction error also signal aversive prediction errors, challenging the dominant theory.

Preliminary results suggest amplitude difference between ERP for delivery and omission of taste. If soon forthcoming main results follow this trend to significance, we will be the first study to show FRN response to both rewarding and aversive taste, using a unimodal stimulus. This is important because using a single primary modality as a stimulus reduces variability between stimuli and between participants, providing an objective method to assess the function of FRN. The results challenge the conventional theory that FRN signals the difference between reward and aversion, instead suggesting that FRN signals the delivery of any salient outcome, be it rewarding or aversive. This has implications for FRN as a signal of salience.

Poster Ref: P1-D-041

Theme: D: Learning, Memory and Cognition

Pre-pulse inhibition (PPI) predicts male and female mice's motor response induced by a low dose of cocaine.

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Prepulse inhibition (PPI) is the normal reduction of the amplitude of the startle reflex in response to an intense startling stimulus (pulse) when this intense stimulus is shortly preceded by a weaker sensory stimulus (prepulse). PPI is modulated by the dopamine system; deficits in this process cause disruption in the information processing and has been shown in people with psychiatric disorders. Previous studies in our laboratory with low doses of cocaine (1 and 6 mg/kg) have shown that low-PPI mice are less sensitive to the reinforcing effects of cocaine in the conditioned placed preference (CPL) paradigm. In consequence, the purpose of the present study was to evaluate the function of PPI as a predictor of the motor effects of a low dose of cocaine (5mg/kg). 24 male and 24 female mice in high- and low-PPI were classified using two pre-pulse (75 and 85 dB) and two inter-stimulus intervals (30 and 100 msec). The spontaneous motor activity was registered during 1 hour (habituation) and during 30 minutes after the administration of cocaine (motor response). During the habituation to the new environment, low-PPI males showed less motor activity than high-PPI males. Moreover, low-PPI females presented higher activity than low-PPI males in this phase. Motor response induced by cocaine was significantly increased in high-PPI males only. Therefore, we can conclude that high-PPI males are more sensitive to the motor effects of the drug, because they show greater motor reactivity to a low dose of cocaine (5mg/kg) than other groups. These results lead us to think that PPI discriminates animals with a higher response to motor effects induced by cocaine. We consider that PPI can be a physiologic marker of vulnerability for cocaine-use disorder, but future studies are necessary with other doses of cocaine for a better understanding.

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Poster Ref: P1-D-042

Theme: D: Learning, Memory and Cognition

The effects of cholinergic lesions of the hippocampus on episodic-like and context-place memory in a new behavioural apparatus.

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Animals' memory can be assessed through their spontaneous exploration of novel configurations of an environment. These types of tasks are used in memory research to develop therapies for memory loss in neurodegenerative diseases. The problem with these tasks is that exploration can be driven by other factors such as the stress that is induced by the amount of handling. In a typical memory task animals only do one trial *per* day, which means that many animals are required to maintain statistical power and accumulation of data is slow.

This study sought to determine how effectively episodic memory can be tested in a multiple trial apparatus in intact and lesion animals. Previous studies have shown that tasks of episodic-like (what-where-which) memory are impaired by lesions of the fornix (Eacott & Norman, 2004) and the hippocampus (Langston & Wood, 2010). However, rats with lesions of the cholinergic projections to the hippocampus perform well on the episodic-like task. Nonetheless they are impaired in a task that involves memory for the conjunction of context and place (where-which) (Easton *et al.*, 2011). Therefore, acetylcholine may only be necessary in some hippocampal-dependent processes.

Here we replicate this earlier finding in an apparatus where multiple trials are run in a single session, meaning a significant (approx. 50%) reduction in animal numbers. The findings demonstrate the reliability of the dissociation within the hippocampus based on cholinergic function within the hippocampus, and verifies the new apparatus as assessing episodic-like memory in the same manner as earlier studies, improving the reliability of the task and having a significant 3Rs benefit.

Eacott, M. J., & Norman, G. (2004). Integrated memory for object, place, and context in rats: A possible model of episodic-like memory? The Journal of Neuroscience, 24(8), 1948–1953.
Easton, A., Fitchett, A. E., Eacott, M. J., & Baxter, M. G. (2011). Medial septal cholinergic neurons are Necessary for context-place memory but not episodic-like memory. Hippocampus, 21, 1021-1027.
Langston, R. F. & Wood, E. R. (2010). Associative recognition and the hippocampus: Differential effects of hippocampal lesions on object-place, object-context and object-place-context memory. Hippocampus, 20, 1139-1153.

Poster Ref: P1-D-043

Theme: D: Learning, Memory and Cognition

Neural basis of the extinction of appetitive conditioning – an fMRI study.

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[1]University of York, [2]Université Lille Nord de France, [3]Universidade do Minho, [4]University of Sheffield

Although vital, both appetitive and aversive Pavlovian conditioning can lead to the development of maladaptive behaviours implicated in a number of psychological disorders. In appetitive conditioning, if the appetitive unconditioned stimulus (US) is a drug, the presence of a conditioned stimulus (CS), i.e., stimuli associated with drug–taking, can trigger drug-cravings, and result in relapse in abstinent users. These conditioned responses (CRs) can be extinguished by repeatedly presenting the CS in the absence of the rewarding US (or aversive US, in the case of aversive conditioning), a process known as extinction. Compared to extinction processes to aversive CSs, very little is known about the neural networks involved in extinction to appetitive CS. Therefore, this study was designed to examine whether the neural networks involved in appetitive and aversive extinction are distinct. We used functional magnetic resonance imaging (fMRI) to examine activation in brain regions during acquisition and extinction of CS associated with either positive or negative outcomes. During the Acquisition phase, two conditioned stimuli (geometrical shapes), CSapp and CSav, were always followed be an appetitive (pleasant images) or an aversive (unpleasant images) US, respectively. Acquisition was immediately followed by an Extinction phase, where the CSapp and the CSav were now always presented in the absence of the US. Successful conditioning and extinction were confirmed by ratings of the pleasantness of the CS during both acquisition and extinction phases: There was a significant increase in likeliness for the CSapp during acquisition and a decrease during extinction; the opposite was the case for the CSav. Bold activation for CSapp was contrasted with activation to the CSav during conditioning and extinction to study the brain areas involved in the extinction of appetitive conditioning. Preliminary results implicate similar neural networks in appetitive and aversive extinction. Clarifying the neural networks involved in appetitive extinction can contribute to the understanding and further development of extinction-based therapies for treatment of drug-dependence.

Poster Ref: P1-D-044

Theme: D: Learning, Memory and Cognition

Dopaminergic modulation of appetitive trace conditioning: the role of D1 receptors in medial prefrontal cortex.

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University of Nottingham

Rationale: Trace conditioning provides a behavioural model suitable to examine the maintenance of 'on line' information and its underlying neural substrates.

Objectives: Experiment la was run to establish trace conditioning in a shortened procedure which would be suitable to test the effects of dopamine (DA) D1 receptor agents administered by micro-injection directly into the brain. Experiment lb examined the effects of the DA D1 agonist SKF81297 and the DA D1 antagonist SCH23390 following systemic administration in pre-trained animals. Experiment 2 went on to test the effects of systemically administered SKF81297 on the acquisition of trace conditioning. In Experiment 3, SKF81297 was administered directly in prelimbic (PL) and infralimbic (IL) subregions of medial prefrontal cortex (mPFC) to compare the role of different mPFC sub-regions.

Results: Whilst treatment with SCH23390 impaired motor responding and/or motivation, SKF81297 had relatively little effect in the pre-trained animals tested in Experiment 1b. However, systemic SKF81297 depressed the acquisition function at the 2s trace interval in Experiment 2. Similarly, in Experiment 3, SKF81297 (0.1µg in 1.0µL) microinjected into either PL or IL mPFC impaired appetitive conditioning at the 2s trace interval.

Conclusions: Impaired trace conditioning under SKF81297 is likely to be mediated in part (but not exclusively) within the IL and PL mPFC sub-regions. The finding that trace conditioning was impaired rather than enhanced under SKF81297 provides further evidence for the inverse U-function which has been suggested to be characteristic of mPFC DA function.

Poster Ref: P1-D-045

Theme: D: Learning, Memory and Cognition

Chronic treatment with topiramate does not reduce the extinction period of CPP induced by cocaine in mice.

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Cocaine dependence is typically a chronic, relapsing disorder. Nowadays, no effective pharmacological treatment exists for cocaine abuse. Topiramate (Topamax®), an anticonvulsant drug that has been used successfully in the treatment of alcohol dependence, has been proposed as candidate for the treatment of cocaine addiction. Topiramate was associated with a clinical improvement in the severity of cocaine dependence, being more efficacious than placebo decreasing craving. However, there are controversial results across studies and it is unclear if topiramate preserves cocaine abstinence. Our goal was to determine the chronic effect of topiramate (100 mg/kg/day) on the extinction phase of the Conditioning Place Preference (CPP) paradigm induced by cocaine (25 mg/kg) in mice. This paradigm evaluates the associative rewarding effects of drugs with environmental cues; and consists in Pre-C phase (natural preference by compartments is recorded), Conditioning (drug is associated with a compartment), and Post-C (reinforcing effect of cocaine is evaluated comparing Pre-C and Post-C scores of the drug-paired compartment). Five days after the end of Conditioning, the CPP extinction phase began and mice started topiramate (n=14) or vehicle (n=13) treatments (2 daily administrations p.o. of 50 mg/kg topiramate or saline every 12h). After 23 days of treatment, the saline group extinguished the preference, while animals treated with topiramate continued maintenance of CPP, showing a preference for the drug-paired compartment. This indicates that topiramate prolongs the extinction phase in comparison with the saline group, and is possibly potentiating the associative effects of cocaine with environment cues. In view of these results, we conclude that topiramate is not effective to block the associative effects of cocaine that induce craving.

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Poster Ref: P1-D-046

Theme: D: Learning, Memory and Cognition

Physiological correlates of trait anxiety in humans and non-human primates.

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High trait anxiety is a risk factor for affective disorders, and is linked to altered prefrontal cortex (PFC) function and biased responding to threat. Investigations of the underlying mechanisms require animal and human studies with directly comparable methods. Studies in non-human primates are vital because of their well-developed PFC; however, most of these focus on responses to predators/human intruders, whilst human studies typically examine responses to more abstract cues or contexts associated with threat. Therefore, we developed translational methods to assess anxious responses to novel, neutral cues presented in a context of unpredictable threat, in high and low trait-anxious humans and non-human primates (the common marmoset, *Callithrix jacchus*). In marmosets, trait anxiety was assessed by the human intruder test, and vigilance to neutral cues was monitored within a context previously paired with unpredictable aversive noise of either moderate or high intensity (moderate-threat or high-threat, respectively). A separate cohort of animals screened for trait anxiety underwent structural magnetic resonance imaging to assess differences in regional brain volume. Low-anxious marmosets showed a rapid habituation of vigilance to neutral cues in the moderate-threat context, but sustained vigilance to such cues in the high-threat context, consistent with proposals that higher state anxiety biases attentional processing towards a greater focus on salient cues. In contrast, high-anxious animals showed sustained cue-directed vigilance even under moderate threat, alongside reduced dorsal anterior cingulate volumes. In humans, self-reported trait anxiety was assessed within the context of competitive sport, an environment that regularly calls for performance under intense anxiety and unpredictable pressures. Responses to neutral cues in the context of unpredictable threat (mild electric shocks) were assessed by eye-blink startle in the Neutral-Predictable-Unpredictable threat test. High trait anxiety was associated with significantly greater startle potentiation by the neutral cue during unpredictable threat. This highlights similarities between trait anxiety in marmosets and humans, and sets the stage for further studies of vulnerability to affective disorders.

Poster Ref: P1-D-047

Theme: D: Learning, Memory and Cognition

Social stress increased ethanol consumption in the two bottle choice paradigm in mice.

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Universidad de Valencia

Exposure to stressors can produce behavioural and neurochemical adaptations that render individuals more prone to drug-seeking and drug-taking behaviours. Alcohol is the most consumed drug of abuse in the USA and Europe and binge drinking is becoming increasingly frequent. Stress experiences are a risk factor for alcohol abuse in humans and recent studies in animal models reported that repeated social stress increased alcohol consumption. The aim of the present work is to evaluate the acute or long-term effects of stress induced by social defeat on the consumption of ethanol (ETOH 6%) using the two bottle choice paradigm. Four groups of adult male mice were used. In the first group mice were exposed to acute social defeat (four episodes on alternative days) immediately before the availability of ETOH (ASD+ETOH). The second group of mice were exposed to intermittent social defeat (four encounters with an aggressive resident mice, one every 72 hours) three weeks before the availability of ETOH (RSD+ETOH). Respective control groups were introduced into a cage without an opponent (NASD+ETOH and NRSD+ETOH). Both types of stress (acute and intermittent) enhanced the consumption of ETOH. Mice exposed to acute social defeat showed this increase with respect to controls only during the stress exposure but not afterwards. Three weeks after exposure to intermittent social defeat, stressed animals showed a higher ETOH consumption than control animals during four weeks. These results suggest that exposure to social stress, besides increasing alcohol intake acutely, can induce long-term effects on the vulnerability to consume alcohol that must be considered for the improvement of prevention and treatment programs of alcoholism.

Acknowledgements: Ministerio de Economía y Competitividad, Dirección General de Investigación, PSI2011-24762, Instituto de Salud Carlos III, Red de Trastornos Adictivos (RTA) RD12/0028/0005. Ministerio de Sanidad, Servicios Sociales e Igualdad. Delegación del Gobierno para el Plan Nacional Sobre Drogas, Proyectos de Investigación sobre Drogodependencias, 2014I007. Generalitat Valenciana, Conselleria de Educación, PROMETEOII/2014/063 and VALi+d (for MP G-P), Spain. The European Foundation for Alcohol Research (ERAB), EA13 08.

Poster Ref: P1-D-048

Theme: D: Learning, Memory and Cognition

Environmental enrichment effects on adult hippocampal neurogenesis in mice: dorsal vs. ventral dentate gyrus.

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Introduction: the hippocampus is a well-defined neuroanatomical structure that may not act as a unit. The dorsal (Septal pole) and ventral (Temporal pole) portions of it are believed to be involved in different processes: long-term memory and hypothalamic–pituitary–adrenal (HPA) axis regulation, respectively. In addition to this, the dentate gyrus (DG) is a well-known source of adult neurogenesis. Our aim was to compare neurogenesis in the dorsal and ventral parts of the hippocampus in both standard and environmental enriched conditions.

Methods: CD-1 female mice (n=96, age 11 weeks) underwent two experimental treatments, ENRICHED and CONTROL environmental conditions. The enrichment condition consisted of i) running wheels, ii) increased space for social activity and iii) dirty bedding coming from C57BL6 male mice. The control condition instead, consisted of standard housing in accordance with the UK's 3Rs guidelines. Experiments lasted 8 days and brains were collected and divided as follows: one third were post fixed in 4% PFA-PBS and used for morphological analyses, one third were processed to quantify neurogenesis-related gene expression and one third was kept for measurement of protein content.

Results: immunohistochemistry for Doublecortin (DCX) revealed that the stained area in enriched animals was larger in the dorsal than in the ventral DG. There was no difference between these two areas in the controls, and stained area was intermediate between dorsal and ventral staining of the enriched animals. Preliminary analysis using a mouse neurogenesis PCR array showed a different pattern of gene expression among the 84 genes screened in dorsal and ventral hippocampus. Analysis of cell proliferation is presently ongoing, as well as analysis of protein levels.

Conclusions: Environmental enrichment increases the DCX positive area in dorsal DG while it decreases in ventral DG. The qPCR assay provided us with other candidate genes to quantify the changes in DG neurogenesis. Molecular quantification of neurogenesis could speed up the study of pathologies in which neurogenesis plays a crucial role (*e.g.* depression, Alzheimer's disease).

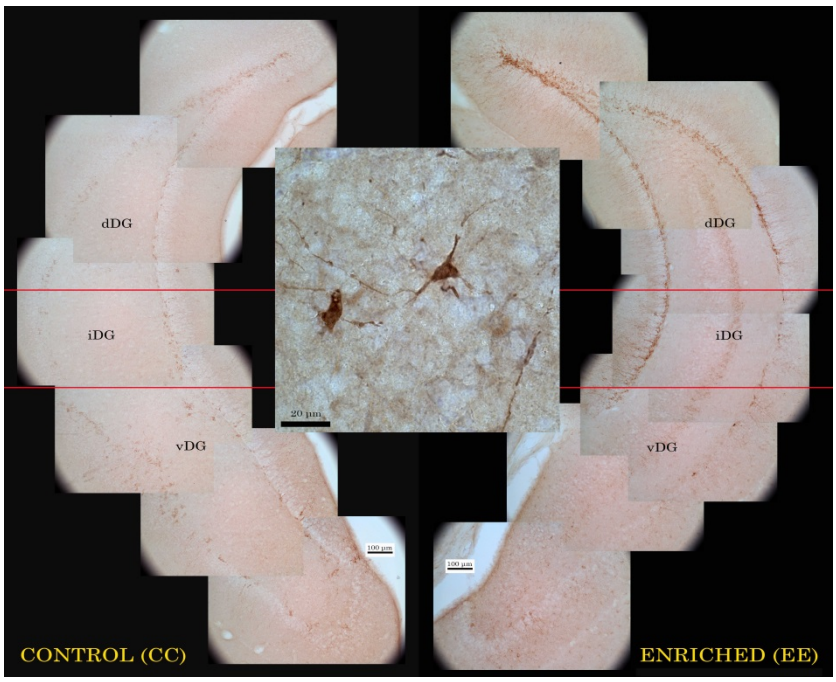

Fig.1 - Environmental effects on mice neurogenesis. Montage of microphotographs (20X) of mice brain coronal section showing hippocampal dentate gyrus region stained for Doublecortin positive cells. Left side represents control group, right side represents enriched group. Overlying central microphotograph represents a higher magnification (100X) of two Doublecortin positive cells.

Poster Ref: P1-D-049

Theme: D: Learning, Memory and Cognition

Social defeat in adult mice increases cocaine conditioned place preference: role of dopamine receptors.

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Stressful experiences contribute to the initiation and escalation of psychostimulant use and may also trigger relapse. Our aim was to evaluate the influence of repeated social defeat (RSD) and dopamine receptor antagonists on the rewarding and reinstating effects of a threshold dose of cocaine in the conditioned place preference (CPP) paradigm. The expression of dopamine receptors D1 (DRD1) and D2 (DRD2) in the cortex and hippocampus was also measured following RSD. A hundred adult male mice of the OF1 strain were used. Mice were exposed to four episodes of RSD; initially the experimental animal was placed in the home cage of the aggressive opponent (10min) protected by a wire mesh. In the second phase, the wire mesh was removed and a 5min confrontation period initiated. In the third phase, the wire mesh was replaced for a further 10min. The exploration group underwent the same protocol, but without the presence of a “resident” mouse in the cage. The D1 (SCH 23390, 0.250 mg/kg) and the D2 (raclopride 0.6 mg/kg) DA antagonists were administered 30 min before each of the social encounters. CPP took place three weeks after the last social defeat, it consisted of three phases: pre-conditioning, conditioning (1mg/kg of cocaine) and post-conditioning. All groups in which CPP was confirmed were subsequently exposed to the extinction procedure. The effects of a priming dose of cocaine were evaluated 24 h after confirmation of extinction. Cerebral cortex and hippocampus samples were analyzed by Western Blot to quantify the DRD1 and DRD2 receptor three weeks after the social defeat procedure. Our results showed that RSD mice developed CPP and that preference was reinstated in these animals. SCH administration during social defeat did not block this preference. In contrast, raclopride blocked CPP in RSD mice. DRD1 levels in the hippocampus were lower after the fourth defeat and returned to normal levels after three weeks. No changes were observed in the cortex. However, DRD2 levels were higher three weeks after the RSD in the hippocampus and cortex, where increases were also observed after the first and fourth encounters. Our results indicate that RSD increases the conditioning rewarding effects of cocaine and that this sensitivity is mediated by the DRD2 receptors.

Poster Ref: P1-D-050

Theme: D: Learning, Memory and Cognition

Dopamine impairs early consolidation but enhances late consolidation of episodic memory.

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Memory consolidation underpins adaptive behaviour, and dopamine networks may be critical for prolonged, selective information storage. Much animal research has found that dopamine has effects when administered during consolidation (Bernabeu *et al.*, 1997; Bethus, Tse, & Morris, 2010; Furini, Myskiw, Schmidt, Marcondes, & Izquierdo, 2014; Péczely *et al.*, 2014). To understand the dopaminergic contribution to memory consolidation in humans, here we investigate the effect of dopamine on recall and recognition in the short and longer term in Parkinson's disease (PD). Fifteen people with PD were each tested on or off dopaminergic medication during learning/early consolidation (day one) and/or late consolidation (day two). Fifteen age-matched healthy participants were tested only once. On day one participants learnt new information and early episodic memory was tested after 30 minutes. Then on day two, recall and recognition were re-tested after a 24 hour delay.

Participants on medication on day one recalled less information at 30 minutes and 24 hours (regardless of dopamine state on day two). In contrast, patients on medication on day two (8-24 hours after learning) recalled more information at 24 hours than those off medication. Although recognition was unaffected by medication, response bias was dependent on dopaminergic state: medication during learning induced a more liberal bias 24 hours later (more 'yes' responses) whereas patients off medication during learning were more conservative responders 24 hours later (more 'no' responses). We use computational modelling to propose a possible mechanism for this change in response bias. In summary, dopamine impairs episodic memory during encoding or early consolidation and makes responses more liberal, but enhances late memory consolidation presumably through a dopamine-dependent consolidation pathway that may be active during sleep.

Poster Ref: P1-D-051

Theme: D: Learning, Memory and Cognition

Implanting artificial associative olfactory memory by targeted activation of single olfactory neurons in *Drosophila* larvae.

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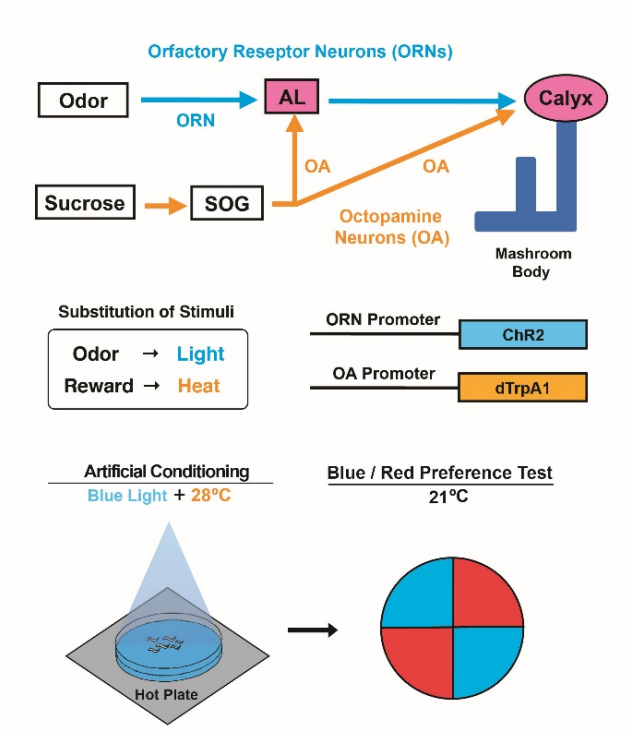
The fruit fly *Drosophila melanogaster* has been used as a model for understanding genetic and molecular basis of learning and memory. Appetitive olfactory memory is formed in the *Drosophila* by at least two sets of external stimuli, conditioned odour stimuli (CS) mediated by the olfactory receptor neurons (ORNs) and unconditioned reward stimuli (US) mediated by the octopaminergic (OA) neurons. Previous studies reported that synaptic output from OA neurons is required for acquisition of appetitive memory in both adult flies and larvae. However, whether associative memory can be induced by targeted activation of only olfactory CS and OA-mediated US pathways remains to be elucidated. Moreover, whether the complex combinatorial signals mediated by the activation of multiple ORNs are necessary to induce distinctive associative memory has not been addressed so far. With its simple neuroanatomical design, the larval brain of *Drosophila* can be utilized as an excellent model system for elucidation of neurocircuitry mechanism of memory. The architecture of the larval brain is a simple extension of the embryonic axonal plan, and the neuronal pathway of olfactory information is straightforward without redundancy. In this study, we applied optogenetic and thermogenetic techniques to analyze the neurocircuitry mechanism of memory induction in the larval brain. We substituted sugar reward stimuli by thermogenetic activation of OA neurons with the dTrpA1 channel, and odour stimuli by optical activation of a specific class of ORNs with Channelrhodopsin-2 (ChR2). We showed that targeted activation of the converging memory circuitry with blue light and heat produces associative memory in the transgenic larvae. Furthermore, we showed that targeted stimulation of only a single type of ORNs is sufficient to induce olfactory memory. We successfully demonstrated that this artificial olfactory memory persists for medium term, and as stable as natural memory produced by the activation of multiple ORNs using a real odorant. At BNA 2015, we plan to show detailed results and further preliminary findings. Given its simplicity and robustness, this new method could be utilized to further our knowledge on the neurocircuitry mechanisms of memory.



Implanting artificial memory in living flies by remote stimulation : we constructed transgenic flies to substitute 1) the reward signals with dTrpA1-mediated thermogenetic activation of OA neurons and 2) the odor signals by ChR2-mediated optical activation of ORN. We showed that targeted activation of OA neurons and only a single type of ORNs is sufficient to form the associative olfactory memory.

Poster Ref: P1-D-052

Theme: D: Learning, Memory and Cognition

Homeostatic maintenance of the microglial population in the healthy brain is achieved through a balance of self-renewal and apoptosis.

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Activation and proliferation of microglial cells has been implicated in a number of chronic neurodegenerative and neuroinflammatory conditions. However, there are many aspects of basic microglial physiology that are poorly defined in the healthy central nervous system. We studied the mechanisms regulating the maintenance of the microglial population in the healthy and ageing brain. We used c-fms EGFP transgenic mice to facilitate microglial identification, combined with assessment of *in vivo* proliferation and microglial homeostasis in models displaying dysregulated apoptosis. We report on the rate and dynamics of microglial division, suggesting that a balance of proliferation and apoptosis of resident microglia are key processes in maintaining the population in the healthy brain. Our data suggest that microglia self-renew over a 16-hour time period, subsequently eliciting apoptosis to regulate population cell numbers. Analysis of mouse models with anti-apoptotic modifications (Bim-/-, Puma-/- and vav-Bcl2 transgenic) support the relevance of microglial apoptosis in maintaining the population dynamics in the adult brain. In particular vav-Bcl2 mice, that have a strong defect in microglial apoptosis, show a time-dependent accumulation of microglial cells, whilst having unaffected neuronal or astrocytic populations, and showing normal behaviour.

In otherwise healthy ageing mice, we observed substantial anomalies in the microglial population. We observed multinucleated aggregates of microglia in healthy aged murine brain. Intriguingly these appear to form from infiltrating bone marrow-derived cells rather than resident microglia undergoing failed cytokinesis, as evidenced by their absence in Ccr2-/- mice.

Finally, using post-mortem human brain samples we observed a significant age-related increase in the total number of microglial cells in the grey matter compared to white matter, suggesting sub-regional variations in population dynamics.

These results highlight a fundamental process in neurobiology, which is key to understanding the physiology of microglial cells. The functional significance of these age-related changes is unknown, however they have implications for our understanding of the role of microglia in the development of age-related neuropathologies.

Poster Ref: P1-D-053

Theme: D: Learning, Memory and Cognition

Prefrontal and accumbal single unit responses encode reward and motor aspects of operant behaviour in rats.

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School of Psychology, University of Leicester

Medial prefrontal cortex (mPFC) contributes to the organisation, planning and execution of responses to behaviourally relevant cues. Rats with lesions in mPFC display a decrease in flexibility and an increase in premature responses in attentional tasks, suggesting that this region plays an important role in execution of favourable and inhibition of inappropriate behavioural responses. Further, a primary projection field of mPFC, the nucleus accumbens (NAc) is involved in reward anticipation, action selection and response inhibition. Populations of NAc neurons are excited or inhibited by reward-predictive cues and temporary inactivation of NAc shell in rats has been shown to impair inhibitory control reflected in an increase of premature responses, whereas inactivation of NAc core decreased accuracy and increased response latency, suggesting a functional sub-division between NAc core and shell. Dysfunction in both mPFC and NAc has been implicated in maladaptive impulsive behaviour as seen in addiction. However, the role of mPFC – NAc interaction in motor response initiation and suppression during reward seeking behaviour has not been studied. To this end, we have developed a discrimination task in which rats were required to either respond or suppress responding to distinct auditory cues in order to obtain a reward. Single unit responses in mPFC and NAc core and shell were recorded during the discrimination task in overtrained rats. Initial results show that single unit responses to trial onset cue in both mPFC and NAc have a clear motor preparation component, but were also modulated by the expectancy of reward.

Poster Ref: P1-D-054

Theme: D: Learning, Memory and Cognition

Exploring the unexplored: neural networks and a common dysfunction across disorders of addiction.

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[1]University of Cambridge, [2]New York University, USA [3]Brighton and Sussex Medical School, [4]Brown University, USA

Tricky decisions arise almost daily, from the mundane, should I try something new for lunch today, to the more exotic, should I move to a different city? Individuals must consider the trade-off between exploring an uncertain environment and exploiting the known, in the hope of maintaining optimal decision-making. Here we map the neural correlates of the exploratory dilemma in healthy volunteers and assess behavioural aberrancy in patients with disorders of compulsivity. Thirty two participants with alcohol use disorders (AUD), 29 obese subjects with binge-eating disorder (BED) and without BED were compared to matched healthy volunteers using a task designed to elicit exploratory or exploitatory choices. We separately collected resting-state functional MRI (rsfMRI) data from 37 healthy volunteers. Traditionally, single-echo planar sequences are used to acquire rsfMRI data. However, these are highly vulnerable to major movement-related artefacts, resulting in much spurious noise. To avoid this poor signal:noise ratio, we employed a novel multi-echo planar sequence allowing a more precise distinction between neuronal (BOLD-like) and non-neuronal (non-BOLD-like) components. In subjects with alcohol use disorders (AUD), exploratory behaviour was reduced across gain and loss environments, in favor of more repetitive or exploitatory choices. Obese subjects with and without binge-eating disorder (BED) do not differ from healthy volunteers in their exploratory choices but when compared to each other there is some divergence within the loss domain. Obese subjects with BED explore more whereas those without BED explore less in the context of loss. We find that more exploratory decisions in the context of reward are associated with frontal polar and ventral striatal connectivity as well as higher long-range connectivity of global neural networks. In the context of loss, exploration is associated with frontal polar and precuneus and lateral orbitofrontal cortex connectivity. We highlight similarities between obesity and substance use disorders to loss-related exploration and elucidate the neural architecture subserving exploration.

Poster Ref: P1-D-055

Theme: D: Learning, Memory and Cognition

Pre-exposure enhances generalization of contextual fear.

Dieuwke Sevenster

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Background: Fear generalization is considered a core mechanism in the development of pathological fear. Previous neutral experiences have been shown to affect subsequent fear generalization. The degree of similarity between the pre-exposure and conditioning context is thought to determine the amount of generalization to that context on later testing.

Methods and Results: In a human fear conditioning paradigm we tested the effect of pre-exposure to a context that is similar to the conditioning context (context A), the conditioning context itself (context B) or a completely different context (context C) on fear generalization. Subjects were exposed to one of the three contexts on day 1. One day later conditioning to context B took place. On the third testing day responding to the conditioning context and generalization to both the similar (context A) and the different context (context C) was tested. We observed that when subjects were pre-exposed to the context that was similar to the conditioning context generalization of threat expectancy to both the similar and the different contexts was enhanced. Pre-exposure to the conditioning context or a completely different context did not result in increased generalization.

Discussion: Differences in neutral experiences previous to conditioning can have major consequences for generalization. Possible underlying mechanisms include the phenomena of pattern completion and pattern separation. During pre-exposure a contextual representation is formed. If the conditioning context is sufficiently similar to the pre-exposure context pattern completion mechanisms will ensure retrieval of the pre-exposure context representation, resulting in an increase of generalization. In contrast, when the contexts differ sufficiently, the conditioning context will be encoded as a separate representation (pattern separation), thereby decreasing later generalization.

Poster Ref: P1-D-056

Theme: D: Learning, Memory and Cognition

The effects of citalopram on fear learning and extinction in mice tested on a discriminative fear-conditioning procedure.

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Department of Experimental Psychology, University of Oxford

Understanding how administration of selective serotonin reuptake inhibitors (SSRIs) affects emotional processing is crucial for reconciling apparently contradictory findings regarding acute SSRI administration. For instance, while acute SSRI administration in healthy volunteers increases the processing of fear stimuli, consistent with reports of a paradoxically heightened anxiety in the early stages of SSRI treatment of anxiety disorders, there are also reports that acute treatment can lead to enhanced positive affective processing.

We investigated the effects of citalopram on an animal model of emotional learning, by testing mice on a discriminative fear-conditioning procedure, in which one auditory cue was paired with an aversive event (CS+) and another auditory cue was not (CS-). We used a 5-day protocol, consisting of a 2-day fear training (conditioning) phase, a fear memory recall (FMR) day, and a 2-day fear extinction phase. During fear training, half of the mice received citalopram and the other half saline just before each session. For the FMR and extinction sessions, each group was then split in two, with one half receiving citalopram before each session and the other half saline.

We found that mice treated with citalopram during training showed enhanced fear learning, as evidenced by stronger CS+/CS- discrimination compared to the control group when tested in a drug-free FMR session. Notably, mice treated with citalopram during training showed bi-directional effects, with higher freezing to the CS+ cue and reduced freezing to the CS- cue compared to saline treated mice. Importantly, we also found that mice receiving citalopram during the extinction sessions exhibited a larger decrease in CS+ evoked freezing compared to mice that received saline during extinction.

In summary, citalopram enhanced fear discrimination learning in an auditory fear-conditioning paradigm by affecting the responses to both the CS+ and CS- cues. Citalopram also facilitated fear extinction.

Poster Ref: P1-D-057

Theme: D: Learning, Memory and Cognition

Midbrain dopaminergic neurons show responses to spatial novelty and activation of afferent dopaminergic fibres in the hippocampus promotes subsequent sleep reactivation and increases spatial memory performance.

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MRC Anatomical Neuropharmacology Unit, University of Oxford,

The coordinated firing of hippocampal pyramidal neurons provides a representation of space in the brain. This representation is also thought important for memory since it is reinstated across repeated exposures to the same environment and different environments are encoded by different representations. However, much is still to be understood about how this important memory circuit makes use of value information. Value information is often associated with the activity of dopaminergic neurons of the ventral tegmental area (VTA) but this is best understood in relation to discreet events. Here we investigate the relationships between the VTA, hippocampus, exploration and spatial memory. We found that midbrain dopaminergic nuclei can respond to the more sustained value related stimulus of spatial novelty. We then went on to show evidence that a dopaminergic projection from the midbrain to the hippocampus plays a role in the modulation of hippocampal memory formation. We performed tetrode recordings in the hippocampus and ventral tegmental area of DAT-IRES-Cre mice injected (in the VTA) with a Cre activated viral construct coding for channelrhodopsin. Mice explored familiar and novel open fields and performed a spatial memory task. Transfected axonal segments were found in the CA1 subfield of the dorsal hippocampus. Photostimulation of this projection during exploration (or learning in the memory task) produced increased hippocampal reactivation of waking firing activity in subsequent sleep (thought important for memory consolidation). Furthermore, this was followed by increased stability of newly learnt spatial representations (Place Field Similarity) along with enhanced behavioural performance in a memory probe test.

Poster Ref: P1-D-058

Theme: D: Learning, Memory and Cognition

Methylphenidate in cognition: improved memory and neural correlates of attention.

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Manchester University

Methylphenidate (MP) is a first line treatment for ADHD. It markedly improves attention, presumably by increasing dopaminergic and noradrenergic neurotransmission *via* inhibition of transporters in the prefrontal cortex and striatum (1). In order to understand effects of MP on cognition, we tested its effects in a task of natural forgetting; the novel object recognition (NOR) test. Female hooded-Lister rats treated with 0.9% saline (n=9) showed no preference for a novel over a familiar object after a 6-hour inter-trial interval (ITI) demonstrating natural forgetting at this ITI. However, animals treated with MP (n=10; 2 mg/kg) spent significantly longer ($p<0.05$) exploring the novel object at the same ITI. This supports an effect of MP to enhance memory by reducing natural forgetting. One way in which MP may produce this effect is by increasing attention during the initial exposure phase, aiding the encoding of object features. Indeed, fMRI studies have shown that MP increases BOLD signal in the prefrontal and posterior parietal cortex in humans during tasks requiring attention (2). However, the effect of MP at the neural level is unknown. Therefore, we investigated the effect of MP on the dorsal attention network (DAN) by inserting silicone multi-electrode recording arrays into the cingulate and posterior parietal cortex of urethane-anesthetised female hooded-Lister rats. Initial results suggest that gamma band coherence in the local field potential is markedly raised between these two regions after MP treatment (1 mg/kg) compared to vehicle (0.9% saline). Overall, these data suggest that MP promotes attention *via* enhanced gamma band communication in the DAN, which has beneficial effects on cognitive performance.

1. Berridge CW, Devilbiss DM, Andrzejewski ME, Arnsten AFT, Kelley AE, Schmeichel B, *et al.* (2006) Biol Psychiatry; 60(10):1111–20
2. Tomasi D, Volkow ND, Wang GJ, Wang R, Telang F, Caparelli EC, *et al.* (2011) Neuroimage;54(4):3101–10

Poster Ref: P1-D-059

Theme: D: Learning, Memory and Cognition

Episodic and contextual memory ontogeny in the juvenile rat.

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Episodic memory is the recollection of unique events, with rich detail of times, places and contextual information. In neurodegenerative disease, particularly Alzheimer's, episodic memory is severely impaired very early on. During development, the ability to recall episodic memories emerges later than other types of memory such as novelty recognition, however this ontogeny in animals is so far unconfirmed. We wish to model the emergence of episodic memory for 2 reasons: firstly it will be invaluable for creating age appropriate animal models of developmental disorders and secondly we wish to use memory ontogeny as a novel tool to investigate the deterioration of this type of memory in later life.

We used a battery of spontaneous novelty detection tasks for rats including basic recognition of a novel object stimulus, associative memory for objects and their locations within space and context, and episodic-like memory. We used Lister Hooded rats throughout our investigation, with each rat only ever tested at one age between p25 and adulthood. The test battery was compressed into a 4 day protocol in order to enable acute testing of rats during restricted developmental time windows. Our data show that at p25, rats are able to perform a simple novelty preference task which indicates that they are able to remember the identity of a previously seen object. Object location within space, and episodic memory developed later at p47-48. However, the task for testing associative contextual memory did not show any definitive ontogenetic pattern. Therefore we instead asked whether animals could ignore context information in a novelty detection task. With this task we demonstrated that rats aged p40 and 41 were unable to dissociate an object from its context, whereas before and after this age they were able to ignore context. It is possible that at this age the entorhinal cortex, responsible for contextual memory, starts to provide input to the hippocampus and allows the animal to incorporate contextual information into hippocampal dependent memories, manifesting in an increased salience and therefore interference of context at this age, similar to an effect seen in human development.

Poster Ref: P1-D-060

Theme: D: Learning, Memory and Cognition

Spatial memory deficits in the HdhQ111 mouse model of Huntington's disease.

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Huntington's disease (HD) is a progressive dominantly inherited CAG repeat expansion disorder, with cognitive decline typically appearing years before motor symptoms. The HdhQ111+/- mouse model has been genetically engineered to contain 111 CAG repeats in the huntingtin gene. The slow progression of symptoms in this model is similar to that seen in HD patients, making it especially suited to u studying early HD deficits. There are currently no therapeutic treatments for HD, however a recent focus on the prodromal disease phase provides a market for cognitive enhancers to be researched as symptomatic treatments.

The HdhQ111 mouse model has already been shown to have early cognitive decline characteristic of HD patients, and a battery of sensitive memory tasks have been developed to examine this deficit in the mouse model. The ability of 5 month old HdhQ111+/- mice and C57Bl6/J Wild Type (WT) mice to identify novel configurations of stimuli in their environment were analysed through four novelty detection tasks, incorporating novel object, place and context information to assess their episodic memory. The results showed no statistically significant difference between the two genotypes in any task due to low performance of the WT mice compared to previous experiments. However, in the task involving the association of objects with their locations in the environment, HdhQ111+/- performed considerably worse that the WT, therefore variations of this task were designed to further test the spatial memory of the mice. WT performed significantly better than HdhQ111+/- in all variations of the spatial tasks, indicating a robust deficit in the spatial memory of the HdhQ111+/- mice at 5 months of age.

Poster Ref: P1-D-061

Theme: D: Learning, Memory and Cognition

A high-fat diet in C57Bl/6 mice induces changes in the hippocampal proteome and compromises episodic memory.

Fiona McLean[1], Rosamund Langston[2], Fiona Campbell[1], Altea Lorenzo-Arribas[1] and Lynda Williams[1]

[1]University of Aberdeen, [2]University of Dundee

A high-fat diet (HFD) is known to cause memory loss in rodents; however, complex, episodic-like memory has not been tested in response to HFD. Episodic memory is the recollection of unique events, with rich detail of times, places and contextual information, which is lost early in Alzheimer's disease. Obesity and type 2 diabetes are associated with increased risk of Alzheimer's disease. To identify a potential link between HFD and episodic memory loss, 12 week old, male, C57Bl/6 mice, were fed either a HFD (60% of energy from fat) or a LFD diet (10% of energy from fat) ad libitum and their memory tested daily for two weeks. We used a battery of spontaneous novelty detection tasks adapted for mice, including basic recognition of a novel object stimulus, associative memory for objects and their locations within space and context, and episodic-like memory. Separate cohorts of mice were killed by exsanguination, under terminal anaesthesia, after 3 days, 1 week or 2 weeks on diet. Brains were rapidly removed and frozen over dry ice and kept frozen at -80 C until the hippocampus was dissected for proteomic analysis. A separate group of mice underwent intraperitoneal glucose tolerance tests (IPGTTs) as a non-recovery procedure.

We found that episodic-like memory, along with associative memory involving places and contexts, was compromised after only one week of HFD. However, the ability to recognise a simple novel object stimulus remained intact throughout testing. IPGTT showed that glucose tolerance was compromised from 3 days onwards on HFD. These results demonstrate that hippocampal function is compromised rapidly by HFD but that perirhinal cortex-based simple novelty was unaffected. Proteomics of the hippocampus revealed changes in a number of proteins associated with neuronal damage after only 3 days on HFD. These data link HFD to rapid induction of glucose intolerance; indices of hippocampal neuronal damage and memory deficit and have implications for the link between diet, obesity and cognitive decline.

Poster Ref: P1-D-062

Theme: D: Learning, Memory and Cognition

ERP specificity and priming effects in judgments of dynamic facial expression.

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Introduction: Facial expressions are inherently dynamic but there are relatively few ERP studies to changes in emotional facial expression. This study examined the specificity of the ERP to changes from a neutral to an angry or fearful (target) expression, and whether this ERP could be influenced by an earlier (priming) facial expression.

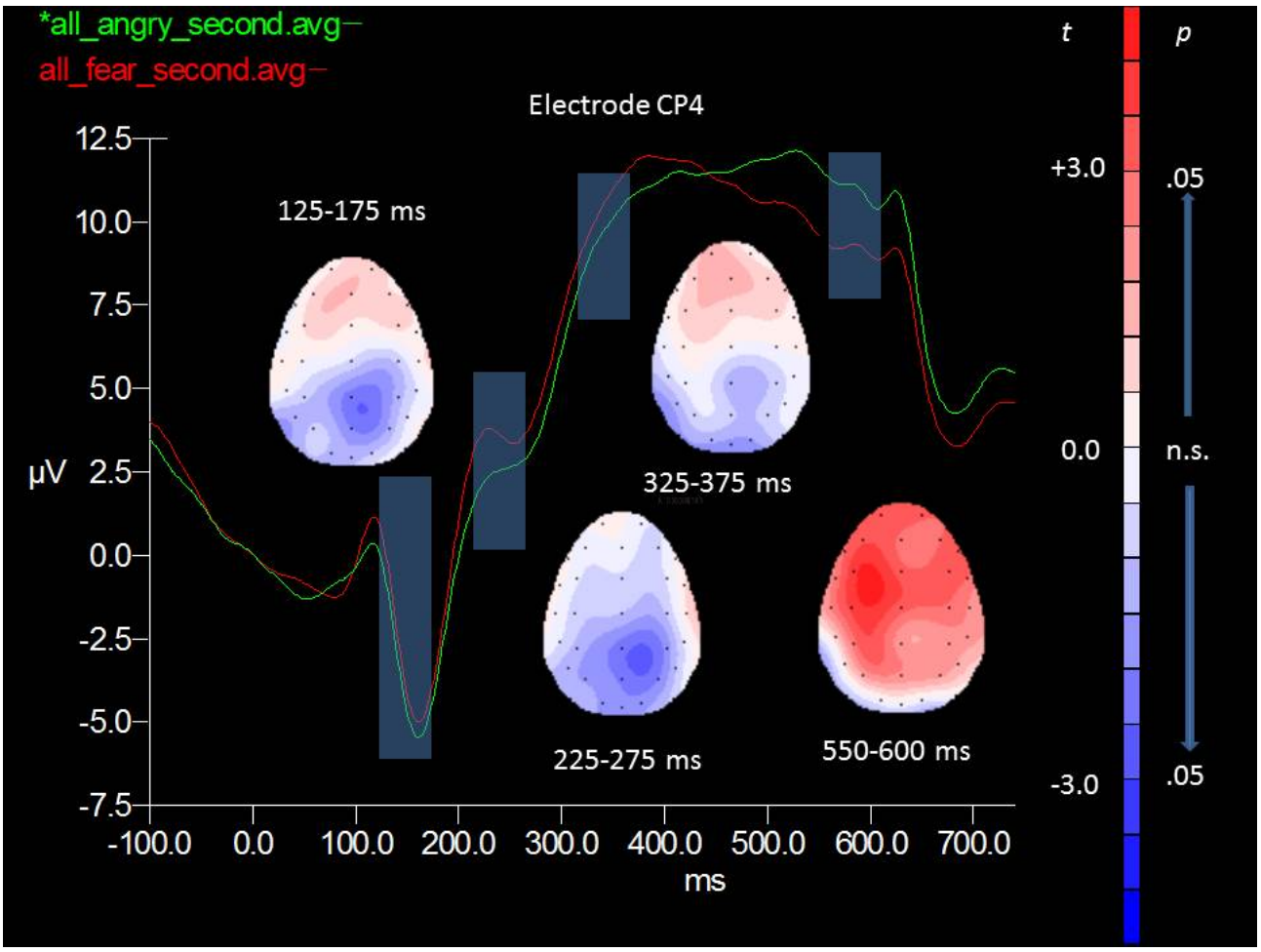
Method: Four stimulus configurations were randomly presented on different trials: angry-neutral-angry, angry-neutral-fear, fear-neutral-angry and fear-neutral-fear. The duration of each stationary expression was 0.5 s and all transitions were instantaneous. Facial identity and viewpoint was constant per trial. For some participants (N=17) the task was to identify the emotional expression in the target interval. For others (N=12), the task was to indicate whether the prime and target emotion was the same or different. All face stimuli and participants were female, average ERPs were recorded conventionally, and peak amplitudes and latencies were measured within predetermined time intervals and electrode groups (ROIs), and analysed using ANOVA.

Results: Significant differences in ERP peak amplitudes to angry and fearful dynamic face targets were found in P1, N170, P2 and P3 ranges, and peak latency differences were significant for P2 and P3. Significant effects of angry versus fearful primes occurred in interaction with the target type, thus the priming emotion modulated the response to the second emotion. This occurred independently of the task, which produced some main effects but did not differentially affect the response to the prime or target emotions.

Discussion: The ERP to a transition between a neutral and an emotional facial expression is more emotion-specific than the ERP to the sudden appearance of a stationary emotional face (Myoshi *et al.*, 2004; Wright, 2007). The present findings demonstrate specificity of ERPs to neutral-angry versus neutral-fearful expression transitions, identifiable across P1, N170, P2 and P3 peak measures. Results also demonstrate the modulating effects of a previous but non-contiguous facial expression.

Myoshi, M., Katayama, J & Morotomi, T. (2004). Neuroreport, 15, 911-914.

Wright, M.J. British Association of Cognitive Neuroscience Annual Meeting, Dundee, August 29-31 2007.



Grand average ERP to the transition from a neutral to an angry face (green trace) or from a neutral to a fearful face (red trace). Data are combined across trials with angry and fearful primes. The scalp maps show t-scores (SPMs) for the differences in mean amplitude within 50ms intervals as indicated. The calibration shows the significance level after an estimated FDR correction.

Theme F: Nervous System Disorders

Posters P1-F-001 to P1-F-058

Poster Ref: P1-F-001

Theme: F: Nervous System Disorders

Investigation of behavioural changes in zebrafish mutant strains: spiegeldanio and odysseus.

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Introduction: spiegeldanio (spd) zebrafish have a mutation in the gene encoding fibroblast growth factor 1a (fgfr1a). Altered Fgf signalling causes a reduction in brain histamine levels and parallel changes to aggression levels. Odysseus (ody) zebrafish have a mutation in the chemokine guidance receptor gene (cxcr4b), which is involved in the migration process of the zebrafish lateral line primordium to form the lateral line system. This subsequently allows deposition of neuromasts for zebrafish to sense water movement. A mutation in cxcr4 therefore leads to an inability to sense water movement in the trunk and tail. The purpose of this project was to gain a better understanding of how alterations to the aforementioned genes can lead to changes in suites of behaviours, thus potentially creating behavioural syndromes.

Methods: Both mutant strains were subject to a number of behavioural assays including: a novel tank diving test for anxiety, a shoaling assay for social interaction and a dominance hierarchy assay to assess for the formation of a dominant-subordinate relationship. Mutant strains were compared to their wild counterparts to assess for any statistically significant behavioural changes.

Results: The novel tank diving test showed significant differences in behaviour between spd and wild-type zebrafish. Mean freezing time of spd mutants was less than that of wild-type counterparts ($p < 0.05$). The shoaling assay showed significant differences in mean cluster score between ody mutants and wild type ($p < 0.01$). Results from the dominance hierarchy assay showed no visible signs of a dominant-subordinate relationship between fish in either experimental group.

Conclusion : Results from the novel tank diving test suggest that spd mutants have reduced levels of anxiety, which may be linked to the reduced brain histamine levels and related to the aggression-boldness behaviour syndrome. However, this would need to be investigated further. According to the shoaling assay, increased levels of aggression, boldness and exploration does not affect social interaction between the same types of fish. The mean cluster score is a rudimentary tool for assessing shoaling and future experiments could use software to measure mean distance between fish at any point in time.

Poster Ref: P1-F-002

Theme: F: Nervous System Disorders

Effects of chemotherapy on association of neural stem cells and neurogenic niche.

Ayesha Maqbool, Annabelle Chambers, Ayoub AL-Bayti and Peter Wigmore

University of Nottingham

Systemic chemotherapy, used in the treatment of cancer, has been shown to produce cognitive deficits in a significant number of patients leading to the coining of the term “Chemobrain”. 5-fluorouracil (5-FU), a cytostatic drug frequently used in the treatment of breast cancer, has been associated with persistent chemotherapy induced cognitive impairments. In animal models, systemic 5-FU treatment produces cognitive impairments and a reduction in cell proliferation in the SGZ of the DG. Prior treatment with the FLX however prevents the cellular and behavioural effects of chemotherapy treatment (Lyons *et al.* 2012).The mechanism of action of 5-FU and FLX on cell proliferation in the SGZ is unclear but may involve changes to the stem cell niche found in the SGZ. Many proliferating cells in the SGZ are associated with micro vascular vessels which may provide support for neurogenesis. We have investigated the impact of acute 5-FU treatment on cell proliferation in the SGZ, micro vascular density and the association of dividing cells with vascular elements with or without chronic FLX treatment. Animals were put down either one day or one week after 5-FU treatment.

4 groups of 8 adult male Lister Hooded rats were used. 1. Saline injection, no FLX; 2. Saline injection, FLX (10mg/kg/day) in drinking water for 3 weeks; 3. An injection of 5-FU (30mg/kg), no FLX; 4. Injection of 5-FU and FLX in their drinking water. Cell proliferation in the SGZ was quantified by Ki67 immunostaining. Microvasculature density was quantified by immuno staining with an antibody against RECA-1 and stereology (ImageJ).

A single dose of 5-FU significantly decreased the number of proliferating cells one day after treatment. Proliferating cell number returned to normal after one week. The proportion of dividing cells not associated with the micro vasculature was more reduced than those on the surface of blood vessels. Chronic FLX treatment prior to chemotherapy prevented the decrease in cell proliferation. Neither chemotherapy nor FLX affected vascular density in SGZ.

Lyons, L., M. Elbeltagy, *et al.* (2012). "FLX Counteracts the Cognitive and Cellular Effects of 5-Fluorouracil in the Rat Hippocampus by a Mechanism of Prevention Rather than Recovery." PLoS One 7(1): e30010.

Poster Ref: P1-F-003
Theme: F: Nervous System Disorders

The effects of chemotherapy and the protective role of antidepressants on white matter tracts in the CNS.

Ayoub Ali Al-Bayti, Valeria Lasio, Maxine Fowler, Ayesha Maqbool, Angus Brown and Peter Wigmore
University of Nottingham

Chemotherapy (chemo) uses cytotoxic drugs to treat cancer. 5-Fluorouracil (5-FU) is an anticancer drug which has been widely used for over four decades in treating various cancers including colorectal, breast, ovarian and oesophageal carcinoma. One of the clinically important adverse effects of chemo, that affects the CNS, is called “chemobrain” and refers to impairments in memory and concentration experienced after chemo (Tannock *et al.*, 2004). Approximately 20–30% of people who undergo chemo experience some level of post- chemo cognitive impairment (Wigmore, 2013).

Although chemo effectively kills cancer cells, it also has side effects on normal cells, especially proliferating precursor and stem cells of the adult brain. Animal models and patient reports have demonstrated changes in conduction properties and the degeneration of white matter tracts after chemo. These changes are likely contributors to post- chemo cognitive decline. We have developed an animal model using Lister Hooded rats to examine the effects of chemo on the corpus callosum and optic nerves. This enabled us to evaluate the impact of systemic chemo on the proliferation of cells and the integrity of the myelin sheath in these two tracts. Following reports of neuroprotection in the hippocampus by the antidepressant Fluoxetine, we determined if this drug would be able to protect white matter tracts from the effects of chemo.

Immunohistochemical analysis showed that both acute (single dose) and chronic (2 weeks)treatment with 5-FU caused a decrease in proliferating cell numbers in white matter tracts. Chronic treatment with Fluoxetine for 3 weeks prior to chemo prevented this reduction in cell proliferation. Transmission electron microscopy showed several abnormal changes of the myelin structures, indicating on-going myelin degeneration after chemo which was prevented by Fluoxetine treatment. This could provide a novel therapeutic approach to reduce cognitive impairment after chemo.

Tannock, I. F., T. A. Ahles, P. A. Ganz, and F. S. Van Dam, 2004, Cognitive impairment associated with chemotherapy for cancer: report of a workshop: J Clin Oncol,v.22,p.2233-9.
Wigmore, P., 2013, The effect of systemic chemotherapy on neurogenesis, plasticity and memory: Curr Top Behav Neurosci, v. 15, p. 211-40.

Poster Ref: P1-F-004

Theme: F: Nervous System Disorders

Microglia regulate hippocampal neurogenesis during chronic neurodegeneration.

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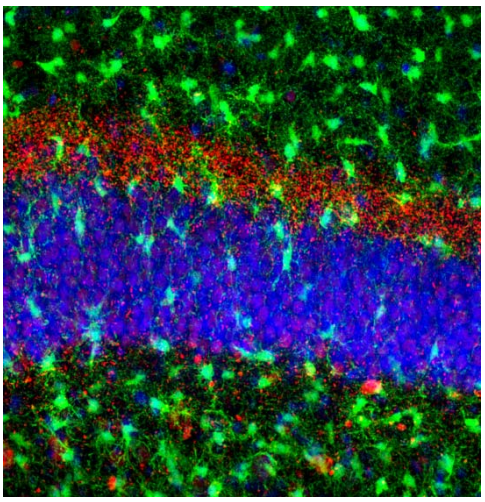
[1]University of Southampton, [2]Université de Mons, Mons, Belgium

Introduction: Adult neurogenesis is responsible for the formation of new neurons in the adult central nervous system. Neurogenesis occurs in at least two niches of the adult mammalian brain and is altered in neurodegenerative disorders; this process is in part regulated by inflammatory factors. Besides neurogenic alterations, neurodegeneration causes a CSF1R-dependent expansion of the microglial population. Our project aims to investigate whether microglia can directly regulate hippocampal neurogenesis in neurodegeneration as well as define the molecular basis of that response.

Methods: We used a multidisciplinary approach combining the analysis of a model of prion disease (ME7) induced in macgreen mice (c-fms EGFP) with immunohistochemistry, retroviral tracing, qPCR, birth-dating and functional inhibition studies.

Results: We found increased hippocampal neurogenesis that correlates with the expansion of the microglia population during prion disease. We observed that after the selective inhibition of microglial proliferation, by the administration of the CSF1R inhibitor GW2580, neurogenesis was reduced. Our data support a role of microglia in driving a pro-neurogenic response, rather than affecting the differentiation and integration of newborn neurons, as evidenced by retroviral tracing. Using a gene screening strategy, we identified the TGF-β pathway as a system controlling the microglial pro-neurogenic response in chronic neurodegeneration.

Discussion: Since inhibition of microglia proliferation caused the inhibition of neurogenesis, we suggest that microglia are responsible for the pro-neurogenic alterations seen in prion disease. We have demonstrated a functional link of the TGF-β pathway with microglial pro-neurogenic activity and identified other candidate inflammatory pathways of interest. Our studies identify CSF1R inhibition as a promising approach to normalizing the conditions of the neurogenic niche during chronic neurodegeneration.



Confocal microscopy image of the dentate gyrus of a macgreen mouse subjected to the ME7 model of prion disease. Microglia are shown in green while the marker calretinin is shown in red.

Poster Ref: P1-F-005

Theme: F: Nervous System Disorders

AUT6, a novel and selective Kv3 channel modulator, alleviates cognitive and neurobiological dysfunction in an animal model of schizophrenia, implications for a new drug treatment for schizophrenia.

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The voltage gated potassium channel Kv3.1, mainly located on parvalbumin (PV) GABAergic interneurons, is closely involved in brain circuitry thought to be affected in schizophrenia. Acute treatment with AUT6, a novel Kv3.1 modulator restores deficits in cognition and social behaviour in the sub-chronic phencyclidine (PCP) rat model of schizophrenia. Kv3 channel modulators may thus provide treatment of these unmet clinical needs in schizophrenia. Our aim here is to explore efficacy of chronic treatment with AUT6, to improve cognitive and neurobiological deficits in the PCP model.

Adult female hooded-Lister rats received PCP (2 mg/kg; n=30) or vehicle (n=10) i.p. for 7 days. After 6-weeks washout, PCP-treated rats received AUT6 (60 mg/kg; p.o.; AUT6; n=10) or vehicle (VEH, n=10 and PCP, n=10) for 21 days or 21 days plus 7 days washout (AUT6wo, n=10). Rats were tested for memory performance in the novel object recognition (NOR) test on days 1, 7, 14 and 21 for all groups, and also on days 22 and 28 for the AUT6wo group. On day 21 (or day 28 for AUT6wo group), rats were sacrificed and PV interneuron density quantified using immunohistochemistry.

A significant deficit in NOR at each time point was observed in PCP group. This deficit was reversed by concomitant AUT6 treatment on days 1, 7, 14 and 21 ($p<0.01$). The reversal of the PCP deficit was no longer observed following 1-day washout in AUT6wo group ($p>0.05$). The NOR deficit was associated with a significant reduction in PV density in the hippocampus ($p<0.01$) and infralimbic cortex ($p<0.05$) in PCP group. As for NOR, this deficit was significantly reduced by AUT6 ($p<0.05$ and $p<0.01$, respectively) and was not observed following a 7-day washout. Kv3.1 channel-positive cells density is currently being assessed.

AUT6 showed efficacy to alleviate the cognitive and neuropathological deficits in a validated animal model of schizophrenia. Efficacy of AUT6 to restore cognitive function was associated with restoration of the PV deficit observed in PCP model. The modulation of Kv3 channels on PV neurons could thus be an important novel approach for the treatment of schizophrenia symptoms and restoration of neuronal function.

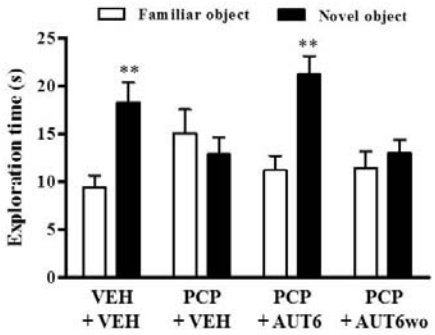

Figure: Efficacy of chronic AUT6 treatment (60 mg/kg, p.o., AUT6) for 21 days or 21 days plus 7 days of washout (AUT6wo) to reverse the deficit induced by sub-chronic PCP (2 mg/kg, i.p., 7 days) in the retention trial in NOR. Data are expressed as mean ± s.e.m (n=10/group) and were analysed by ANOVA and Student's t-test. **p<0.01; significantly different from the familiar object.

Poster Ref: P1-F-006

Theme: F: Nervous System Disorders

A computational study of stimulus driven epileptic seizure abatement.

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Active brain stimulation to abate epileptic seizures has shown mixed success. In spike-wave (SW) seizures, where the seizure and background state were proposed to coexist, single-pulse stimulations have been suggested to be able to terminate the seizure prematurely. However, several factors can impact success in such a bistable setting. The factors contributing to this have not been fully investigated on a theoretical and mechanistic basis. Our aim is to elucidate mechanisms that influence the success of single-pulse stimulation in noise-induced SW seizures.

In this work, we study a neural population model of SW seizures that allows the reconstruction of the basin of attraction of the background activity as a four dimensional geometric object.

For the deterministic (noise-free) case, we show how the success of response to stimuli depends on the amplitude and phase of the SW cycle, in addition to the direction of the stimulus in state space. In the case of spontaneous noise-induced seizures, the basin becomes probabilistic introducing some degree of uncertainty to the stimulation outcome while maintaining qualitative features of the noise-free case. Additionally, due to the different time scales involved in SW generation, there is substantial variation between SW cycles, implying that there may not be a fixed set of optimal stimulation parameters for SW seizures.

In contrast, the model suggests an adaptive approach to find optimal stimulation parameters patient-specifically, based on real-time estimation of the position in state space. We discuss how the modelling work can be exploited to rationally design a successful stimulation protocol for the abatement of SW seizures using real-time SW detection.

Poster Ref: P1-F-007

Theme: F: Nervous System Disorders

Behavioural characterisation of a potential mouse model of severe intellectual disability and autism.

Jilly Hope, Jennifer Doig, Dinesh Soares and Cathy Abbott

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Intellectual disability, epilepsy and autism are largely distinctive but frequently co-occurring neurological disorders for which there is a major lack of effective treatments. Here, we have a group of newly discovered dominant missense mutations in a translation elongation factor gene, eEF1A2, through which patients present with all three disorders, providing an excellent opportunity to study the underlying mechanisms. As part of my PhD project I aim to characterise a potential mouse model of this novel syndrome, which has a heterozygous loss of function mutation in eEF1A2, to determine whether there are any behavioural phenotypes consistent with intellectual disability and/or autism. This has involved a wide range of different behavioural tasks, such as the Y-maze, novel object recognition test, marble burying test and stranger mouse task, which have aided our investigation into the consequence of the mutation i.e. whether or not it results in loss of protein function, and allowed us to determine whether this mouse could be used as a model of the human condition. The evidence so far suggests that only aged heterozygotes have learning and memory deficits, as shown by the novel object recognition data. In contrast, the stranger mouse task showed that heterozygotes have social discrimination deficits at all ages. Future work will involve the generation of mice with the same missense mutations found in the patients and a behavioural comparison will be performed between these newly generated mice and the mice tested here.

Poster Ref: P1-F-008

Theme: F: Nervous System Disorders

Examining whether serum from a patient with anti-NMDA receptor encephalitis contributes to the aberrant morphology of cells in an associated teratoma.

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Anti-NMDA-R encephalitis presents with an aggressive autoimmune response and severe neuropsychiatric symptoms. Antibodies specific to the NMDA-R bind to the NR1 subunit and promote cross linking and receptor endocytosis (Hughes *et al.*, 2010). In women anti-NMDA-R encephalitis is sometimes associated with an ovarian teratoma raising the possibility that NMDA receptors expressed therein generate an autoimmune response (Dalmau *et al.*, 2007).

We characterised an ovarian teratoma from a patient with anti-NMDA-R encephalitis, which exhibits areas of robust staining with GFAP antibody and prominent choroid plexus tissue. The latter is only present in 5% of all teratomas. Despite these indications of neural tissue, labelling by the neurone specific MAP2 and synaptophysin antibodies was absent. H and E staining revealed that GFAP positive tissue is encompassed by inflammatory cells. Further analysis revealed that inflammatory cells were positive for markers of T lymphocytes, B lymphocytes and leukocytes. Strong punctate labelling with an NR1 subunit antibody is evident within areas where inflammatory cells meet GFAP positive tissue. Additionally there is evidence of intranuclear vacuoles indicative of autophagy and cell death.

We investigated the effects of serum from the same patient on receptor trafficking and cell viability using a mouse fibroblast L(tK-) cell line stably expressing dexamethasone-inducible recombinant NR1A/NR2A NMDA-Rs (Priestley *et al.*, 1995). Initially the NR1 antibody and patient serum labelled surface receptors. However, after more prolonged exposure the serum became intracellular and the cells exhibited morphological changes reminiscent of those in the teratoma, with deformed nuclei. These data suggest that the serum may contribute to the aberrant morphology of GFAP positive cells in teratoma tissue.

A detailed analysis of teratomas associated with anti-NMDA-R encephalitis may provide insights into mechanisms contributing to this debilitating disease.

Poster Ref: P1-F-009

Theme: F: Nervous System Disorders

Kainate receptors and brain diseases: linking genetics, electrophysiology, and pharmacology.

Maria Koromina[1], John William Grzeskowiak[1], UK10K Consortium[2], Douglas Blackwood [3], Ian Mellor[1] and Helen Miranda Knight[1]

[1]University of Nottingham, [2]UK10K (www.uk10k.org), [3]University of Edinburgh

The glutamate system is the main excitatory neurotransmitter system of the brain and involves three classes of ionotropic glutamate receptors: NMDA, AMPA and kainate receptors. In this project we focus on kainate receptors (KARs), which are composed of tetrameric combinations of five subunits (GluK1-5) to form functional ion channels. These receptors are involved in short term synaptic plasticity mechanisms, synaptic integration and long-term modulation of neurotransmission. Genetic variants identified within genes which encode for the KAR subunits are reported to contribute to risk for genetically complex brain disorders such as epilepsy and neuropsychiatric phenotypes [1]. For example, an insertion deletion variant in GluK4 which we identified as protective against mood disorders [2].

We have used two complementary approaches to investigate the role of KARs and brain diseases. The first approach consists of bioinformatic analysis of next generation exome sequencing data and the interpretation of how functional coding variants may contribute to neuropsychiatric diseases in humans. The second approach involves electrophysiological recording techniques of cloned KAR subunits using *Xenopus* oocytes and treatments with pharmacological agents. We report the identification of a number of predicted damaging missense mutations found exclusively in the case population as well as a nonsense mutation which is predicted to stop the translation of GRIK1 (GluK1) gene. We also report our functional findings of GluK2 and GluK4. Our ultimate goal is to compare wild type and mutated KAR subunit ionic currents and the effect of active compounds on their function. This research will contribute to a better understanding of the link between genetic risk, biological processes and potential therapeutic avenues for brain diseases.

References

1. Hoischen, A. *et al.*, Prioritization of neurodevelopmental disease genes by discovery of new mutations. Nat Neurosci, 17: 6: 764-72, 2014. ISSN 1546-1726.

2. Knight, H. M. *et al.*, GRIK4/KA1 protein expression in human brain and correlation with bipolar disorder risk variant status. Am J Med Genet B Neuropsychiatr Genet, 159: 1: 21-9, 2012. ISSN 1552-485X.

Poster Ref: P1-F-010

Theme: F: Nervous System Disorders

The relationship of prion protein aggregate size and conversion potential in two different idiopathic human prion diseases.

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National CJD Research & Surveillance Unit, University of Edinburgh

Background: Human prion diseases are fatal neurological disorders characterised by the conversion of the normal host prion protein (PrPC) to a misfolded infectious protein (PrPSc), which deposits in the brain. Sporadic Creutzfeldt-Jakob disease (sCJD) and a novel prionopathy, variably protease-sensitive prionopathy (VPSPr), are idiopathic forms of the disease. The range of PrPSc aggregate sizes in prion diseases is wide, but little is known about the biological properties of differently sized PrPSc aggregates in prion propagation.

Aims: We aimed to compare the seeding ability of sCJD and VPSPr PrPSc using an *in vitro* conversion assay. We also determined the seeding activity of PrPSc aggregates fractionated according to their size and density.

Methods: Brain tissue from patients with sCJD, VPSPr and a non-prion disease control were analysed. sCJD and VPSPr brain homogenates were analysed by Western blot for protease resistant PrPSc (PrPres). Sucrose density gradient centrifugation (SDGC) was used to separate PrPSc aggregates according to their size and density. Real-time quaking induced conversion (RT-QuIC) was used to assess seeding activity.

Results: Both sCJD and VPSPr samples seeded conversion in RT-QuIC. However, seeding activity, normalised for PrPres amount, was lower for VPSPr. Following SDGC, the majority of PrPres from both sCJD and VPSPr samples sedimented to the bottom of the gradient, although the seeding activity was detected throughout the density gradient.

Conclusion: The ability to convert PrPC *in vitro* is shared by sCJD and the newly described human prion disease, VPSPr. Both VPSPr and sCJD aggregates are heterogeneous in size and their seeding activity is found distributed across a wide range of PrPSc size classes with the greatest converting activity per unit of PrPres associated with the smaller aggregates.

Poster Ref: P1-F-011

Theme: F: Nervous System Disorders

Amyloidogenic prion seeds, alone, are not sufficient to trigger neurodegeneration.

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Aberrant folding of host encoded proteins is common across many neurodegenerative diseases, acting as seeds for the "prion-like" propagation of normally folded protein to abnormal conformations. Such diseases include Alzheimer's disease, Parkinson's disease, prion diseases, amongst many others. Misfolded proteins are regarded as causal factors of pathology, defining neurodegeneration based on selective spread around the brain. Their role in neurodegeneration, however, remains unanswered. We addressed this question using recent technological advances in the sensitive detection of misfolded protein species acting as prion seeds.

In contrast to generally accepted selective spread of misfolded proteins, prion seeds were widespread, distributed independently of neurodegeneration. Transcriptional regulation of stress pathways were concurrently observed across all brain regions tested, indicating impaired homeostasis resulting from prion seed exposure. Despite this, neurodegeneration and inflammatory responses were restricted to specific brain regions. We demonstrate that misfolded protein capable of seeding is insufficient, alone, to initiate a neurodegenerative cascade. Instead multiple non-cell autonomous factors are required to act additively to trigger neurodegeneration.

Poster Ref: P1-F-012

Theme: F: Nervous System Disorders

Development of whole brain organotypic slice culture to model amyloid plaque formation.

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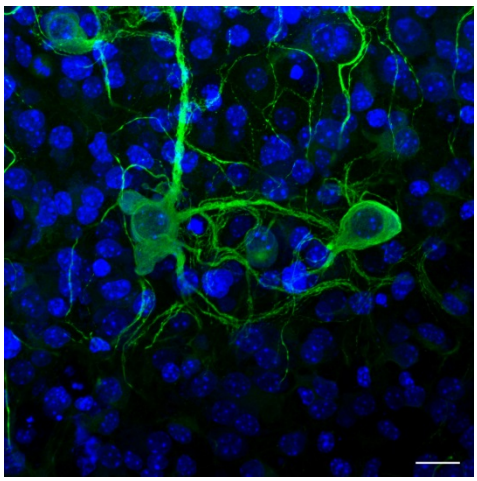
The mechanism of amyloid plaque formation in protein misfolding neurodegenerative diseases, including Alzheimer's disease and Prion diseases remains largely unknown. In these diseases several different protein conformation species exist as precursors to plaque formation, including monomers, oligomers and fibrils. The identity of the toxic species in Alzheimer's disease and prion disease is yet to be specified; however oligomeric species are currently the prime candidate (1).

In this study, whole brain organotypic slice culture (BOSC) has been utilised to enable real-time modelling of plaque formation dynamics in Alzheimer's disease and prion disease models *in vitro*. Using a combination of LI-COR and confocal imaging systems, we will examine the molecular and cellular events leading to plaque formation within BOSC following exposure to prion infected brain homogenate, recombinant prion protein fibrils and beta amyloid seeds.

Brain slices have been characterised and maintained in culture for 8 months. We are able to image specific cell populations such as neurons and glia using confocal microscopy. This will allow us to identify changes in cell morphology in response to pre-formed seeds which are currently being prepared. We will also assess the effect of exposure to different pre-formed amyloid seeds and amyloid accumulation on cell survival within BOSC. To compare plaque formation *in vitro* and *in vivo*, multi-photon microscopy will be used to image the brain of a transgenic mouse model of beta amyloid accumulation.

This study aims to elucidate the mechanisms of plaque formation and moreover will provide groundwork for future therapeutic advancements by allowing a greater understanding of the toxic or protective effects of plaque formation.

1. Taylor *et al.*, (2002) Toxic proteins in neurodegenerative disease. Science 296, 1991



Maximum projection confocal image of neuronal and nuclear staining in the hippocampal region of a whole brain organotypic slice using anti-MAP2 Kinase antibody (green) and fluorescent nuclear marker TOPRO-3 (blue). Taken using a Zeiss 710 confocal microscope using a x40 oil objective, scale bar: 20µm.

Poster Ref: P1-F-014

Theme: F: Nervous System Disorders

Gradient in network oscillation properties along the dorsal-ventral axis of the medial entorhinal cortex is impaired in rodent model of tauopathy.

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The entorhinal cortex provides the main interface between the hippocampus and the cortex. It is one of the first areas to be affected in Alzheimer's disease. Neurones in the medial entorhinal cortex (mEC) display a dorsal-ventral gradient in a number of neurophysiological properties ranging from intrinsic excitability and action potential properties in stellate cells to 'grid cell' spacing - the functional output by which certain mEC cells respond in specific spatial locations within an environment. This study explores the network dynamics of mEC gamma oscillations (30-100Hz) recorded electrophysiologically both *in vitro* and *in vivo* from 7-9 month old, male Tg4510 and wild-type (Wt) littermate control mice. The former is a model of tauopathy produced by transgenic overexpression of a repressible tau variant responsible for the familial neurodegenerative tauopathy FTDP17 in man[1].

Synchronous network oscillations in the gamma frequency band were reliably induced in parasagittal mEC slices by application of low concentrations (200-500 nM) of kainic acid. Oscillations were observed simultaneously at both dorsal and ventral recording sites. In Wt slices, a dorsal-ventral gradient was present in both the frequency and power of oscillations, with faster and greater amplitude activity observed in dorsal mEC. This gradient was diminished in Tg4510 mice, with changes in gamma oscillation properties preferentially affecting the dorsal mEC. We next determined whether these deficits were present in an intact system by chronically implanting 16-channel linear silicon probes along the dorsal-ventral axis of the mEC of Tg4510 and Wt control mice. A dorsal-ventral gradient in the power of gamma frequency network activity was observed in Wt mice *in vivo*, when running at a constant speed on a linear track. In comparison, gamma frequency network activity in the mEC was impaired in Tg4510 mice.

Deficits in network activity in this dementia model could have functional implications for grid cell properties in the entorhinal cortex. A flattening of the observed dorsal-ventral gradient may disrupt the formation of a 'cognitive map' and thus contribute to an impairment of spatial information processing in dementia.

1. Ramsden, M. *et al* (2005). J. Neurosci. 25, 10637–47

Poster Ref: P1-F-015

Theme: F: Nervous System Disorders

CB1 receptor modulation of transmission at mouse neuromuscular junctions in a simple model of neuromuscular weakness.

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Endocannabinoid system (ECS) modulation of synaptic transmission in the mammalian CNS generally involves cannabinoid CB1 receptors. Here its function and potential as a target for treating neurodegeneration, pain and mental illness have been widely explored. Recently, the CB1R agonist ACPA was found to inhibit neuromuscular transmission at lizard and frog neuromuscular junctions (NMJs). If present at mammalian NMJs, the ECS may prove a useful treatment target for diseases such as congenital myasthenia and failing transmission in motor neurone disease. Here, we look for evidence of the ECS at NMJs in mammals.

After ethical killing (ASPA, 1986; 63/2010/EU), diaphragms from adult male MF1 mice (30-45gm) were excised and bathed in physiological saline at room temperature. After ensuring healthy neurotransmission (nerve-evoked contraction > 95% muscle-evoked contraction), twitch and tetanic tension in muscle strips was reduced by ~50% by low Ca^{2+} (0.5mM) and raised Mg2+ (1.2-3mM) to assay CB1 ligand effects on nerve-evoked contraction. In paralysed hemidiaphragm/phrenic nerve preparations, synaptic potential modulation was monitored in normal Ca^{2+}/Mg^{2+} with sharp intracellular electrodes.

0.1 - 10μM ACPA produced a dose-dependent inhibition ($P<0.0001$, Two-Way ANOVA) of nerve-evoked twitch tension, by up to 48.7 ± 5.6% (mean ± SE), and tetanic tension (50Hz, 0.5s), by 14.4 ± 1.3% (both n=4), vs vehicle control (DMSO, n=8) at 10 μM, reaching significance at 0.2μM ($P<0.03$, Bonferroni post-hoc). ACEA, another CB1R-selective agonist, had similar effects. ACPA's inhibition was abolished by 10μM AM251 (CB1R antagonist/inverse agonist, n=9). Cannabinoids had no effect on direct muscle-evoked muscle tension. Evoked postsynaptic potentials were reduced by 19% by ACPA (n=3), and increased by 48% by AM251 (n=4), during 2 min, 20Hz stimulation trains (two-way ANOVA, both $P<0.001$).

This is the first evidence that CB1 receptors are functionally important at mammalian NMJs. The data suggest the receptors can strongly modulate neuromuscular transmission, and hence might be a novel therapeutic target for agonists, inverse agonists or allosteric modulators to treat neuromuscular diseases involving perturbed neurotransmission.

Poster Ref: P1-F-016

Theme: F: Nervous System Disorders

Neuroprotective effects of melatonin and/or calpeptin administered after onset of reperfusion in a rat model of transient focal cerebral ischemia.

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Introduction: Melatonin is a potent antioxidant. Previously, we have demonstrated beneficial effects of pretreatment with melatonin in rodent models of focal cerebral ischemia (Pei, Pang, & Cheung, 2002). Cerebral ischemia increases intracellular concentration of calcium ion and activates several calcium dependent proteases such as calpain. Calpeptin is a novel calpain inhibitor. The aim of this study is to investigate the neuroprotective role of melatonin and/or calpeptin administered after onset of reperfusion in transient focal cerebral ischemia.

Method: Male Sprague Dawley (SD) rats weighing 250-280 g underwent right-sided endovascular middle cerebral artery occlusion (MCAO) for 90 minutes following by 24 hours of reperfusion. An intracerebroventricular injection of vehicle, melatonin and/or calpeptin were initiated 10-15 min after the onset of reperfusion. Regional cerebral blood flow (rCBF) was monitored using a laser Doppler flowmeter. Cerebral infarction volumes were evaluated using tetrazolium staining and analyzed by Image J software. Neurological behaviour was assessed using Neurological Deficit Scoring System (NDSS) test.

Results: Treatment with either melatonin or calpeptin reduced the corrected ipsilateral hemispheric infarction volumes and NDSS score in a dose-dependent manner. Compared with the control group, the corrected ipsilateral hemispheric infarction volumes and edema ratio were significantly reduced by high dose calpeptin (50 microgram/kg). Although medium dose calpeptin (15 microgram/kg) and low dose melatonin (50 microgram/kg) did not significantly reduce infarction volumes when injected individually, the combination of the two treatments exerted synergistic effects.

Reference

Pei, Z., Pang, S. F., & Cheung, R. T. (2002). Pretreatment with melatonin reduces volume of cerebral infarction in a rat middle cerebral artery occlusion stroke model. J Pineal Res, 32(3), 168-172.

Poster Ref: P1-F-017

Theme: F: Nervous System Disorders

Melatonin as a neuroprotective therapy against intracerebral hemorrhage.

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Intracerebral hemorrhage (ICH) is a form of stroke caused by bleeding within the brain parenchyma. Patients with ICH may suffer from severe neurological sequels like motor deficits and cognitive impairment. In addition, its mortality rate is much higher than that of ischemic stroke. However, the therapeutic options available for the ICH patients remain very limited. Our work aims to explore an effective treatment for this devastating disease. In the present study, ICH was induced in the rat by intrastriatal injection of collagenase type IV. At 24 h after the ICH induction, the body weight of the rats decreased and hematoma was found in the brain parenchyma. The rats also had neurological deficits. The peri-hematomal tissue was collected for further analysis, and the expression of ED-1 increased. As ED-1 is a marker of activated microglia, its upregulation may suggest exacerbated neuroinflammation after ICH. We believe that inflammation is an important cause for the ICH-induced brain damage. Thus, we further investigated whether melatonin, a potent antioxidant and free-radical scavenger with strong anti-inflammatory actions, could promote recovery after ICH. Repetitive melatonin intraperitoneal injections were given to the rats at 2, 24 and 48 h after ICH, and they were sacrificed at 72 h. The protective effects of melatonin on the neurological deficits were assessed by the rotarod test and neurological deficit scoring system (NDSS). In the future study, we would like to study the anti-inflammatory and other possible mechanisms of melatonin which may be beneficial in ICH.

Poster Ref: P1-F-018

Theme: F: Nervous System Disorders

An omega-3 fatty acid as a novel therapeutic agent for acute intervention after traumatic brain injury.

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Every 90 seconds someone is admitted to hospital in the UK with acquired traumatic brain injury (TBI), more than a million people a year. This represents an increase of 33.5% compared to the previous decade. Currently, there are no specific therapeutic interventions for TBI and clinical management is limited to reduction of the intracranial pressure and symptomatic relief. TBI is associated with a rapid onset of a neuroinflammatory response (delayed secondary injury events), following a primary mechanical insult. The secondary injury represents a window of opportunity for therapeutic intervention; however, despite extensive efforts to develop neuroprotective therapies, there have been no successful outcomes in human clinical trials to date. Docosahexaenoic acid (DHA) is an omega-3 fatty acid that is the most abundant fatty acid in the brain. Previous studies have shown that acute DHA treatment has neuroprotective effects in several acute central nervous pathologies such as stroke and spinal cord injury.

Our research objective was to examine whether the acute administration of DHA after TBI could reduce the acute inflammatory response, which could improve functional outcome after TBI.

A controlled cortical impact (CCI) model of TBI was used in male adult CD1 mice. Mice received intravenously (i.v.) 500 nmol/kg DHA or vehicle (0.2% v:v ethanol in saline) , half an hour after the injury, and all animals received an intraperitoneal (i.p.) injection of the tracer 5-bromo-2-deoxyuridine (BrdU; 50 mg/kg, twice a day) to label dividing cells. The modified Neurological Severity Score (mNSS) was assessed on day 1, 3, 5 and 7 post-injury. On day 7 the brains were harvested for immunohistochemistry and for assessing the lesion volume.

This study shows modulatory effect of DHA on glial response and neurons as well as on levels of oxidative stress. DHA treated animals developed a considerable smaller brain lesion compared to vehicle. All animals showed moderate impaired neurological function after trauma, but there was an improvement on motor function in treated animals. To conclude, we suggest that DHA could serve as a pharmacological approach to minimize the inflammatory responses and enable a less hostile environment for regenerative growth and recovery.

Poster Ref: P1-F-019

Theme: F: Nervous System Disorders

A murine model of neuroinflammation reveals CCR2-independent resolution.

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The Roslin Institute, University of Edinburgh

Chronic non-resolving inflammation is implicated in chronic neurodegeneration and excessive tissue-damaging inflammation exacerbates acute brain injury. Understanding the mechanisms that resolve deleterious inflammation in the CNS is imperative to develop new therapeutic strategies. Current knowledge is limited, in part because of a lack of tractable models. Our aim was to develop a model of self-limiting CNS inflammation that is optimised to address mechanisms controlling resolution, with an initial focus on key contributions and interactions of myeloid cells.

Intracerebral inflammation was induced by stereotaxic injection of bacterial endotoxin and flow cytometric analysis of brain cell suspensions performed at 1-28d post-injection. The kinetics of neutrophil influx and clearance demarcated clearly defined phases of inflammation initiation, propagation and resolution, and was used to define a quantitative resolution index. Proliferation of resident brain macrophages (microglia) preceded the resolution phase, although activation (CD45 and F4/80 intensity) was maximal during resolution. Bone marrow chimaeric (Csf1r-EGFP· WT) and monocyte reporter (Ccr2RFP/+) mice showed monocyte infiltration, differentiation and proliferation contributed to expansion of the total mononuclear phagocyte population coinciding with the resolution phase. Rapid loss of monocyte-derived macrophages and a slow decline in microglial numbers to baseline occurred after resolution. The chemokine receptor CCR2 was dispensable for monocyte recruitment and resolution of the inflammatory response, suggesting Ly6Clo monocytes as potential regulators of resolution.

These data show that subsets of myeloid cells of distinct origins act in a CCR2-independent manner, and are essential for resolving acute inflammation in the brain. This work also establishes a model system to identify endogenous mechanisms preventing progression to chronic neuroinflammation and to test CNS-targeted pro-resolution agents.

Funded by BBSRC and MRC.

Poster Ref: P1-F-020

Theme: F: Nervous System Disorders

Mice hemizygous for a gene implicated in schizophrenia show hyperactivity and attentional deficits that improve with minocycline.

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Developing effective therapies to treat psychiatric disorders relies on good, translational animal models. However, with genetically complex conditions such as schizophrenia it is unfeasible to recapitulate the entire symptomatology in one model so a genetic manipulation approach is often utilised to target specific candidate gene(s). We investigated mice hemizygous for Map2k7 (Map2k7+/-), a gene which is functionally associated with schizophrenia (Winchester *et al*, 2012), by examining their performance in the 5-choice serial reaction time task (5-CSRTT) for attention before and after administration of minocycline, an antibiotic currently showing promise in clinical trials for schizophrenia, and the psychotomimetic ketamine, an NMDA receptor antagonist. We also tested Map2k7+/- mice on the open field (OF) with and without ketamine in order to look at their activity levels.

In the 5-CSRTT, Map2k7+/- mice showed an attentional impairment by missing significantly more trials than WTs ($F(1,154)=42.36$; $p<0.001$). % missed showed improvement after minocycline treatment, from Map2k7+/-:17.8±3.1% to 11.8±1.7%; WT:12.6±1.3% to 10.1±1.7% ($F(2,53)=6.29$; $p<0.01$). Ketamine increased the number of premature responses in all mice ($F(1,59)=12.24$; $p<0.005$) indicating impulsivity, which is also a symptom of schizophrenia, but this effect did not interact with genotype ($F(1,59)=1.08$; $p=0.307$).

Map2k7+/- mice showed hyperactivity compared to WTs in the OF without ketamine ($F(1,18)=13.46$; $p<0.002$), but presented similarly increased hyperactivity as WTs in response to ketamine with no genotype interaction effect ($F(1,18)=0.46$; $p=0.507$). Therefore, NMDA receptors may not be involved (or are compensated for) in molecular underpinnings of Map2k7 hemizygosity and the resulting behavioural phenotype.

Overall, Map2k7+/- mice display attentional deficits in the 5-CSRTT that improves with administration of minocycline, and are more hyperactive in the OF than their WT littermates, an observation made in other, well-known models of schizophrenia (Imre *et al*, 2006). Although further work is required, our results show promise for Map2k7+/- mice being an informative and translatable model of some symptoms of schizophrenia with potential for aiding development of improved therapies in the future.

Poster Ref: P1-F-021

Theme: F: Nervous System Disorders

Atomoxetine restores the response inhibition network in Parkinson's disease.

Charlotte Rae[1,2,3,4], Cristina Nombela[1], Patricia Vazquez Rodriguez[1], Zheng Ye[1], Laura Hughes[1,2], Simon Jones[1], Timothy Ham[1], Timothy Rittman[1], Ian Coyle-Gilchrist[1], Ralf Regenthal[5], Barbara Sahakian[6,7], Roger Barker[1], Trevor Robbins[6,8] and James Rowe[1,2,6]

[1]Department of Clinical Neurosciences, University of Cambridge, [2]Medical Research Council Cognition and Brain Sciences Unit, Cambridge, [3]Brighton & Sussex Medical School, Brighton, [4]Sackler Centre for Consciousness Science, University of Sussex, [5]Rudolf-Boehm-Institute of Pharmacology and Toxicology, University of Leipzig, Germany, [6]Behavioural and Clinical Neuroscience Institute, Cambridge, [7]Department of Psychiatry, University of Cambridge, [8]Department of Experimental Psychology, University of Cambridge

Response inhibition is impaired in Parkinson's disease. On a stop signal task, patients show longer stop signal reaction times (SSRTs), and abnormal responses in regions critical for action stopping, including the inferior frontal gyrus (IFG), preSMA, and subthalamic nuclei (STN).

Animal models indicate an important role for noradrenaline in response inhibition. Loss of noradrenergic neurons, and alterations in fronto-striatal white matter connectivity, may contribute to the impairment. Conversely, the noradrenaline reuptake inhibitor atomoxetine might improve interactions in the response inhibition network in Parkinson's disease.

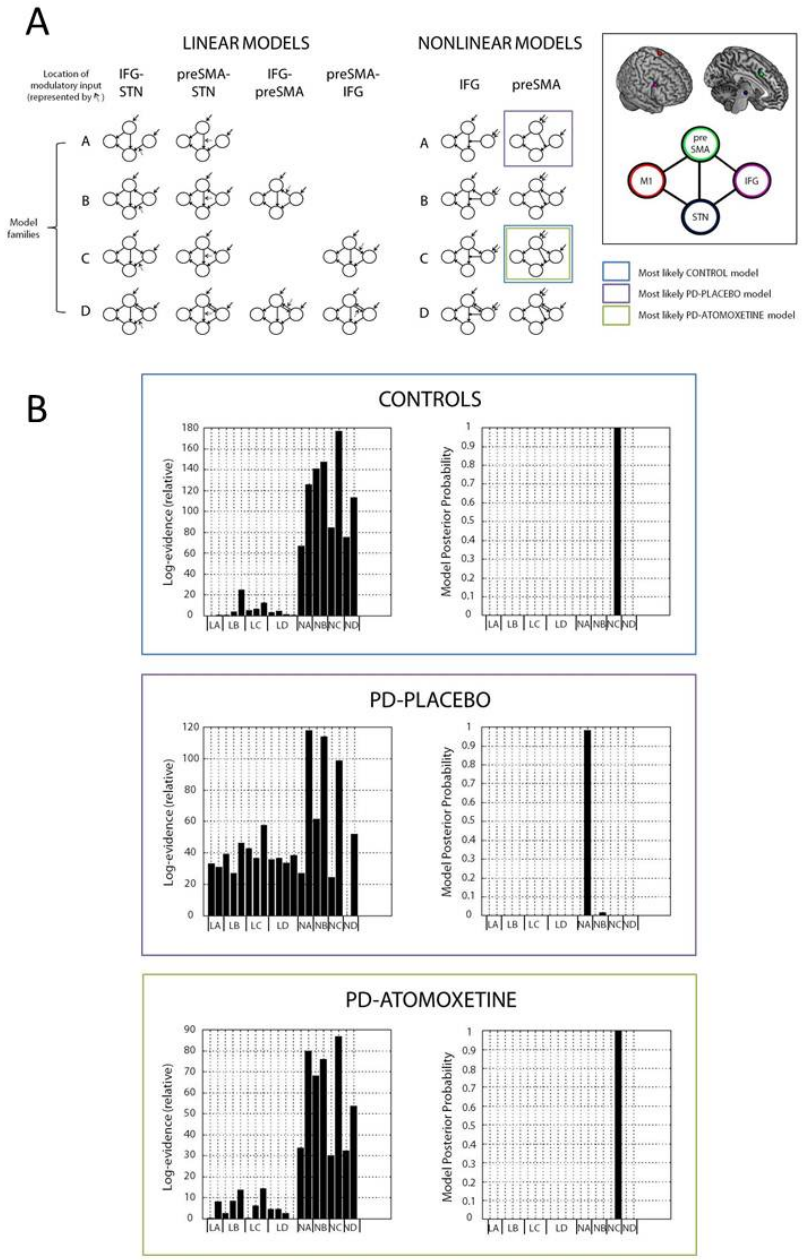
In a double-blind randomized placebo-controlled crossover design, 19 patients with idiopathic Parkinson's disease underwent fMRI during a stop-signal task on two sessions: placebo or 40mg atomoxetine. 20 healthy age-matched controls took part in a single MRI session.

We used Dynamic Causal Modelling (DCM) to investigate effective connectivity, determining how interactions within the response inhibition network become dysfunctional in Parkinson's disease, and how they are influenced by atomoxetine. We applied a DCM analysis inverting a set of 20 plausible models that had previously been studied in healthy young subjects, including interactions amongst key regions of the response inhibition network: the IFG, preSMA, and STN (Fig 1a).

We used Bayesian Model Selection with model-evidences to identify the most likely network in each group and drug session. In Parkinson's disease on placebo (purple, Fig 1b), a cortical interaction between the IFG and preSMA that is present in healthy controls (blue, Fig 1b) is lost. However, atomoxetine restores this interaction (green, Fig 1b).

Individual patient differences in treatment response can vary widely. In multiple regression models, disease severity (UPRDS-III) and blood plasma drug levels predicted frontal-STN connectivity. Restoration of cortical connectivity predicted change in SSRT between placebo and drug sessions. Fronto-striatal white matter connectivity, assessed by diffusion tensor imaging, further predicted change in SSRT with atomoxetine.

These data indicate a potential role for noradrenergic drugs for behavioural symptoms in Parkinson's disease, as an adjunct to dopaminergic medication.


A
LINEAR MODELS
NONLINEAR MODELS
Location of modulatory input (represented by)
IFG-STN
preSMA-STN
IFG-preSMA
preSMA-IFG
IFG
preSMA
Model families
A
B
C
D
pre SMA
M1
IFG
STN
Most likely CONTROL model
Most likely PD-PLACEBO model
Most likely PD-ATOMOXETINE model
B
CONTROLS
PD-PLACEBO
PD-ATOMOXETINE
Log-evidence (relative)
Model Posterior Probability
LA LB LC LD NA NB NC ND

Poster Ref: P1-F-022

Theme: F: Nervous System Disorders

Novel insights into maladaptive behaviours in Prader-Willi Syndrome: serendipitous findings from an open trial of vagus nerve stimulation.

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Background: We report striking and unanticipated improvements in maladaptive behaviours in Prader-Willi Syndrome (PWS) during a trial of Vagus Nerve Stimulation (VNS) initially designed to investigate effects on the over-eating behaviour. PWS is a genetically-determined neurodevelopmental disorder associated with mild-moderate intellectual disability and social and behavioural difficulties alongside a characteristic and severe hyperphagia. The central involvement of the vagus nerve in satiety, together with serendipitously-observed weight loss during Vagus Nerve Stimulation Therapy® (VNS; Cyberonics, TX, USA) for epilepsy and depression, suggested that enhancing vagus nerve signalling could be beneficial.

Methods: Three individuals with PWS underwent surgery to implant the VNS device. VNS was switched on three months post-implantation, with an initial 0.25mA output current incrementally increased to a maximum of 1.5mA as tolerated by each individual. Participants were followed up monthly.

Results: VNS in these individuals with PWS, within the stimulation parameters used here, was safe and acceptable. However, changes in eating behaviour were equivocal. Intriguingly, unanticipated, though consistent, beneficial effects were reported by two participants and their carers in maladaptive behaviour, temperament and social functioning. These improvements and associated effects on food seeking behaviour, but not weight, indicate that VNS may have potential as a novel treatment for such behaviours.

Conclusions: We propose that these changes are mediated through afferent and efferent vagal projections and their effects on specific neural networks and functioning of the autonomic nervous system and provides new insights into the mechanisms that underpin what are serious and common problems affecting people with intellectual disabilities generally.

Poster Ref: P1-F-023

Theme: F: Nervous System Disorders

The role of synapses in neurodegeneration due to mitochondrial disease.

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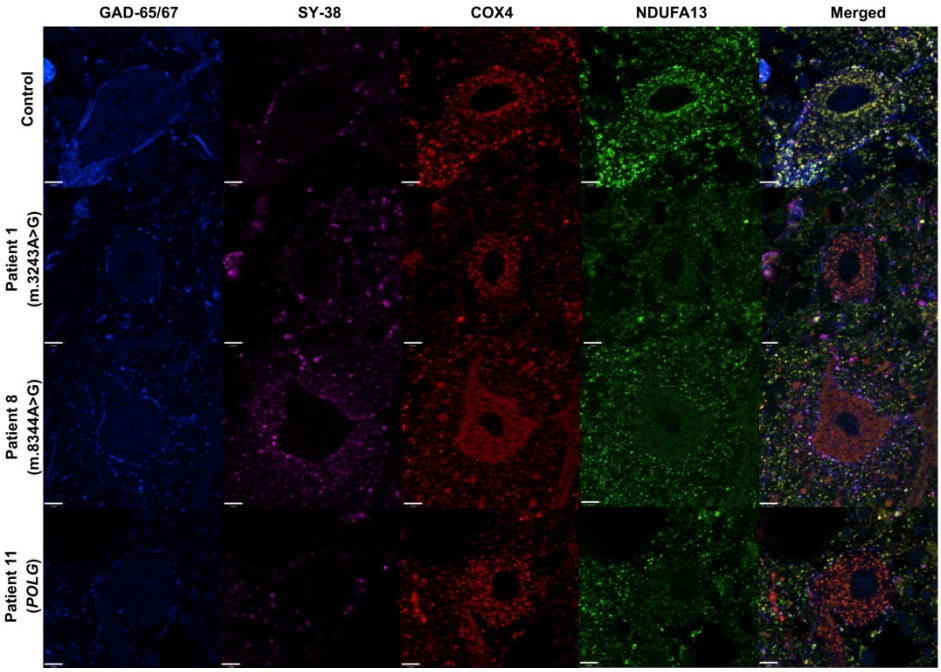
Introduction: Mitochondria are organelles found in every enucleated cell of the body, serving to provide the bulk of energy requirement in the form of ATP. Energy production is achieved through the electron transport chain located in the inner mitochondrial membrane *via* a process known as oxidative phosphorylation (OXPHOS). OXPHOS is under the dual genetic control of nuclear and mitochondrial DNA (mtDNA), hence mutations in either of the two results in energy production defect. MtDNA mutations (either primary or secondary) lead to a heterogeneous group of disorders, known as mitochondrial diseases. These are defined by multi-system involvement with characteristic neuromuscular features. Approximately 70% of patients present with cerebellar ataxia, a neurological condition where motor coordination and balance are impaired. Previous neuropathological studies show severe neuronal loss, respiratory chain deficiency in remaining neurons and synaptic pathology throughout the olivocerebellar pathway.

Aims: Synapses constitute a metabolically active part of neurons, making this neuronal compartment an interesting candidate for further investigation. This study aims to quantify mitochondrial protein expression in Purkinje cells and their inhibitory projections on to the dentate nucleus.

Methodology: A quantitative quadruple immunofluorescence technique was developed to measure respiratory chain protein expression (NDUFA13) in neuronal cell bodies and GABAergic presynaptic terminals in cerebellum sections from 12 patients with mitochondrial disease and 10 age-matched controls (Figure 1). Confocal microscopy was employed for neuronal sampling and enabled three-dimensional reconstruction of inhibitory synapses.

Results: Significant reduction of complex I expression was observed in Purkinje cells and their inhibitory presynaptic terminals in patients. The severity of deficiency between the two sub-neuronal compartments is comparable. Analysis of synaptic density and morphology revealed fewer, enlarged synapses in patients.

Interpretation: This work suggests altered intracerebellar wiring in patients with mitochondrial disease and provides important insights into the neurodegenerative processes taking place.



Quadruple immunofluorescence of cerebellar Purkinje cells. GAD-65/67 is used to detect GABAergic cell bodies and inhibitory synapses. COX4 is a mitochondrial mass marker and NDUFA13 protein is used to detect complex I deficiency. Control Purkinje cells demonstrate co-localisation of COX4 and NDUFA13 protein, while NDUFA13 protein is significantly reduced in patient Purkinje cells. Scale bar:7μm.

Poster Ref: P1-F-024

Theme: F: Nervous System Disorders

Blood pressure disorder and the cognitive profile of Alzheimer**'s disease patients.**

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Alzheimer's disease (AD) is an age-related neurodegenerative disorder affecting 850,000 people in the UK alone (Alzheimer's Society, 2014). The only treatment currently prescribed to patients is for symptomatic relief, and recent attempts at developing disease modifying treatments have been disappointing (Franco & Cedazo-Minguez 2014). As the prevalence of AD is set to increase with the world's ageing population, other factors which may contribute to this multi-factorial disease must be addressed. Many age-related dementias are suspected to have a vascular component; age-related deterioration of cerebral blood vessels (Kalaria, 1996), hypertension (Gifford *et al*, 2013), and arteriosclerosis (Kalaria *et al*, 2012) have all been associated with cognitive impairment. Hypertension in mid-life is associated with increased risk for AD (Qiu *et al*, 2005) however, the effect of blood pressure in old age and after an AD diagnosis is less clear. Hypertension increases in prevalence with age, and can often be controlled with lifestyle factors such as diet and exercise, or with well-tolerated medication. Unlike other underlying causes of dementia, hypertension has successful treatment strategies and known associations with other conditions which may contribute to poor brain health. Therefore understanding more about its role in AD is a worthwhile endeavour. Long-term hypertension may lead to a chronic inflammatory response which is also associated with AD-pathology and symptoms (Krstic & Knuessel, 2013). This retrospective study aims to uncover the effect of blood pressure on cognition in persons diagnosed with AD. AD patients recruited from South East NHS memory clinics were invited to complete a session of cognitive testing, blood pressure measurements and blood sampling. GP surgery data was accessed for previous blood pressure readings. It is hypothesised that those with a history of blood pressure disorder will have a higher inflammatory state, and lower scores on cognitive tests, independent from pre-morbid IQ or age. This is one of the only studies to assess the effect of blood pressure on multiple cognitive domains in AD. Increasing our understanding of the effect of blood pressure in an ageing system may lead to additional treatment or preventative options.

Poster Ref: P1-F-025

Theme: F: Nervous System Disorders

Acidosis-induced cytotoxic mechanisms in neonatal rat astrocytes.

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Cells switch to anaerobic glycolysis when there is a lack of oxygen during brain ischemia. Extracellular pH thus drops and such acidosis causes neuronal cell death. The fate of astrocytes, mechanical and functional partners of neurons, in acidosis is less studied. Our data show that cultured neonatal rat astrocytes suffered cell death after challenge by acidic pH (6.8, 6.0, 5.0) for 2-24 h. Exposure to acidic pH caused Ca^{2+} release and Ca^{2+} influx, but abrogation of cytosolic Ca^{2+} elevation by BAPTA did not prevent acidic pH-induced cell death, hence ruling out the role of Ca^{2+} overload. Acidic pH caused p38 MAPK activation, Akt inhibition, mitochondrial depolarization, decreased reactive oxygen species (ROS) formation and increased ADP/ATP ratio. Cyclosporin A, which binds to cyclophilin D and hence inhibits the mitochondrial permeability transition pore (PTP), could prevent acidity-induced cell death. Our results therefore suggest acidotic astrocyte death was attributable to perturbed p38/Akt signaling and PTP opening.

Poster Ref: P1-F-026

Theme: F: Nervous System Disorders

Haplotype analysis of multiple VNTRs in the MAOA gene as an aid to better understanding of gene x environment interactions in mental health.

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The regulation of MAOA gene expression is a critical determinant of the concentration of monoamines in the CNS. Research has focused on a polymorphic variable number tandem repeat domain termed the μ (μVNTR) as a modulator of this expression. The repeat copy number of the μVNTR is correlated with both differential gene expression and correlation to behavioural disorders. In this study we focus on the contribution of an upstream second VNTR in the promoter position that could modify the action of the μVNTR. This second relatively unexplored marker, here termed distal VNTR (dVNTR), has 7-11 repeats of a core 10bp element.

229 paediatric saliva DNA was obtained from the Wirral Child Health and Development Study (WCHADS) cohort. A customised PCR assays was especially designed and optimised for the dVNTR, while a reference published assay was employed for the typing of the μVNTR. DNA samples were genotyped using a combination of gel and capillary electrophoresis.

Observed alternative alleles were four (3R, 3.5R, 4R, 5R) and three (9R, 10R, 11R) with μVNTR and dVNTR, respectively, while frequency and distribution of allele of μVNTR, 3R 36%, 3.5R 1.25%, 4R 60% and 5R 9% for the dVNTR 9R 75.2%, 10R 22.4% and 11R 7%. The alleles did not vary significantly between males and females ($p>0.05$). Genotypes for the reference and main variant alleles were initially employed for assessing linkage disequilibrium (LD), rare alleles were then incorporated for the construction of the haplotype blocks. Although there was significant LD between both markers, our preliminary data supports the utilisation of the haplotypes of both d- and μ-VNTRs rather than solely that of the μVNTR for stratification analysis of this gene with behavioural traits and clinical outcomes. This latter data will be presented on the poster.

Poster Ref: P1-F-027

Theme: F: Nervous System Disorders

Pathway and regional heritability study of major depressive disorder in Generation Scotland sample.

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Background: Major depressive disorder (MDD) is modestly heritable. The largest genome-wide molecular studies for MDD published so far did not identify replicated loci. Pathway analysis tests for the association or enrichment of variants in pathways with traits. Extended from SNP heritability, the estimation of regional heritability is proposed to detect genetic effects from small genomic regions.

Method: In this study, we first applied pathway analysis methods to unrelated individuals (t<=0.025) in two independent samples. GS:SFHS (Generation Scotland, N=6455) and PGC (Psychiatric Genomics Consortium MDD1,N=18755), for MDD. GS:SFHS is a Scottish Family Health Study. PGC is population-designed study for mega-analyses of genome-wide genetic data for psychiatric disorders. Using GREML method, we then estimated the regional SNP-heritability from candidate pathways and genes in the pathways that are associated with MDD in pathway analysis. Finally, PGRSs from SNPs in candidate pathways were created to compare the risk predicting power with PGRSs based on whole genome SNPs for MDD.

Result: In pathway analysis, 9 pathways were significantly associated with MDD in at least one sample, including NETRIN1 SIGNALING pathway and its sub-pathway, ROLE OF SECOND MESSENGERS in NETRIN1 SIGNALING pathway, in GS:SFHS and PGC sample, respectively. In regional heritability analysis for GS:SFHS sample, 5/9 pathways obtained a significant regional SNP-heritability for MDD. Among them, NETRIN1 SIGNALING pathway obtained the highest estimate of regional heritability (h2=0.014,LRT Pval=0.009). Gene heritability from DCC and UNC5D, 2 receptor genes in NETRIN1 SIGNALING pathway, were detected in MDD. In risk prediction analysis, PGRS based on NETRIN1 SIGNALING pathway explained a higher proportion of variances compared with it based on whole genome variants.

Conclusion: These post-GWAS analyses suggest NETRIN1 SIGNALING pathway is a candidate pathway for MDD. Further replication of regional heritability detected in this pathway in an independent sample is needed.

Poster Ref: P1-F-028

Theme: F: Nervous System Disorders

Modelling the synaptic code for autism spectrum disorders: neuroligin/neurexin axis.

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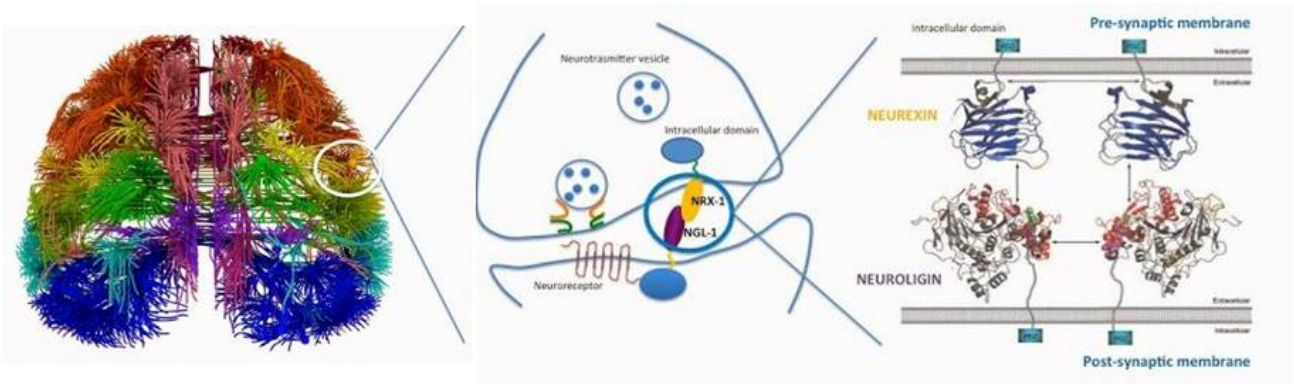
Neuroligins are cell adhesion proteins that interact with neurexins at the synapse. This interaction may contribute to differentiation, plasticity and specificity of synapses. In humans, mutations in neurexin and neuroligin-encoding genes lead to neurodevelopmental disorders including autism and/or schizophrenia. For these reasons applying efforts to understand the key pieces within the neuroligin/neurexin axis we focus attention on molecular components that will subserve credible targets for drugs for these currently intractable conditions. *Caenorhabditis elegans* is an excellent model system to address what is happening in an “autistic synapse”. Its nervous system consists of a defined set of 302 mapped neurons and their patterns of synaptic connectivity are well characterized. This provides an excellent model to investigate the impact of genetic mutations on synapse formation and function to understand the synaptopathies underpinning autism; a platform to identify signalling components that emanate from the neurexin/neuroligins axis using established approaches that allow investigations across the gene to behaviour domains.

We use *C. elegans* as a model to measure how its neuroligin and neurexin genes organize synapse and generate aberrant behaviour, when mutated. In particular we have identified behavioural deficits in *C. elegans* neuroligin mutants. Specifically, through robust enough assays to allow investigation of key signalling pathways, we have established that these mutants in key determinants of autistic traits in humans generate disruption in integrative sensory behaviour. Furthermore, we have been able to re-introduce the human homologues of this gene to rescue against these genetic perturbations, such as food-dependent behaviours. Finally, through transcript analysis we highlight nlg-1 splice variants that change the intracellular domain of the gene product NLG-1. Interestingly, exon 14 is a cassette that encodes a SH3 binding domain, suggesting that the loss of this exon impacts on the NLG-1 competence to recruit intracellular binding partners. This evidences a putative conservation in the intracellular scaffolding recruitment between *C. elegans* and humans.



Location of neuroligin and neurexin at the synapse

Poster Ref: P1-F-029

Theme: F: Nervous System Disorders

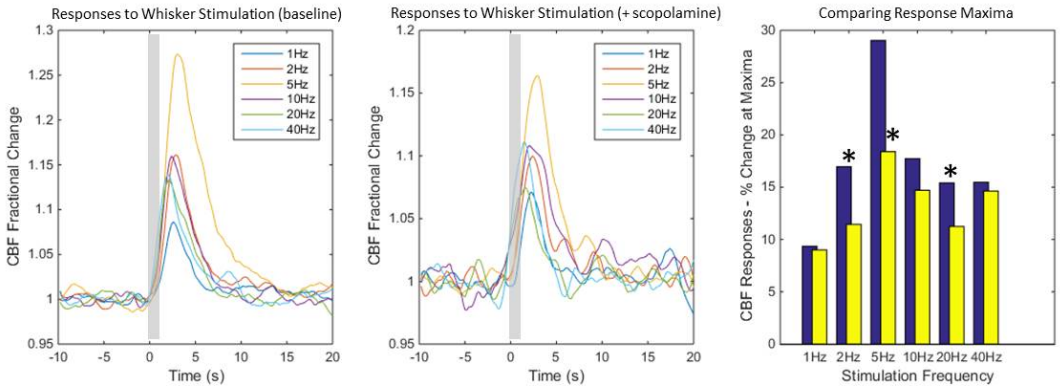
Cholinergic modulation of neurovascular coupling and neuroimaging signals.

Gaia Brezzo, Aisling Spain and Chris Martin

The University of Sheffield

In recent years a growing number of brain diseases have become associated with pathological changes in blood flow regulation and the neurovascular apparatus that supports it. A hypothesis emerging from this work is that interventions to improve neurovascular function may have beneficial impacts upon brain health and may offer some degree of neuroprotection in the face of neurodegenerative diseases. A recent study (Kocsis *et al.*, JCBFM, 2014) suggested that the cognitive enhancement effects of CNS cholinergic drugs were mediated by their vascular rather than neuronal actions. An important question is how these manipulations affect neurovascular coupling, in terms of the rapid adjustment of cerebral blood flow to changing neuronal demands. To investigate this, we used a rodent model in which brain blood flow and neuronal activity were measured across a range of sensory stimulation parameters. In anaesthetised animals, a thin cranial window was prepared over the somatosensory barrel cortex (whisker area) to enable recording of cerebral blood flow using laser speckle contrast imaging. In some animals a burr hole was made in the thin cranial window to allow the insertion of a recording electrode for electrophysiological recording of neuronal activity. Various whisker stimulation protocols were applied including a mixed frequency design (1-40Hz range, 2s duration) and long duration stimulation (5Hz, 16s). Data were acquired at baseline and following the administration of cholinergic drugs, including scopolamine (2mg in 1ml, IV).

Results indicate that cholinergic manipulations alter neurovascular coupling parameters, for example by changing the magnitude of cerebral blood flow responses across a range of stimulus inputs (see Figure). These findings have important implications for (i) our understanding of how drugs which modulate vascular function can impact upon neurovascular coupling and (ii) the interpretation of functional brain imaging signals acquired in the context of cholinergic manipulations, where the assumption of a stable relationship between neuronal and haemodynamic (e.g. BOLD signal) changes, may not be valid.



Cerebral blood flow (CBF) responses recorded from rodent somatosensory cortex in response to a 2s whisker stimulation across a range of stimulation frequencies (n=4). Left: Responses before drug administration; Centre: Responses after scopolamine (2mg i.v.); Right: Comparing response maxima pre- and post-drug. Asterisks indicate $p<0.05$ (related ttest).

Poster Ref: P1-F-030

Theme: F: Nervous System Disorders

Cannabidiol protects against amyloid beta peptide-mediated attenuation of LTP *via* a mechanism independent of 5HT1A receptor activation.

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Cannabidiol (CBD) is a non-psychoactive constituent of marijuana that is presently being investigated as a potential therapeutic agent. It has been shown to reduce amyloid beta (Abeta) mediated neurotoxicity. We have reported that CBD can protect against the neurotoxic effects of Abeta in acute hippocampal slices. Prior treatment of slices with CBD before the addition of Abeta can rescue long–term potentiation (LTP) (Hughes *et al.*, 2012). CBD has been reported to act as a 5HT1A agonist (Legerwood *et al.*, 2011). In this study, we have investigated if the acute neuroprotective effects of CBD are mediated *via* activation of the 5HT1A receptor Using electrophysiological techniques, extracellular field EPSPs were recorded in the CA1 region. Hippocampal slices were prepared from C57/Black6 mice (6-12 weeks). Following a recovery period, stable fEPSPs were recorded for at least 20min. LTP was induced *via* high frequency stimulation (HFS) of the Schaffer-collateral pathway (HFS; two stimulus trains at 100Hz for 1s, with an inter-train interval of 30s). The effects of 500nM Abeta peptide (in the form of amyloid derived diffusible ligands) and also pre-treatment with CBD (10microM) and or the 5HT1A antagonist WAY100135 (300nM) prior to application of Abeta were examined. Acute CBD treatment had no effect on the level of LTP compared to control. Abeta treatment caused a depression in LTP. Pretreatment with CBD prior to Abeta application attenuated the suppressive effect of Abeta on LTP. LTP levels recorded in the presence of WAT100135 were similar to control. Application of WAY100135 for 10 min prior to CBD did not alter the neuroprotective effect of CBD on Abeta-mediated depression of LTP. This data suggests that the neuroprotective effect of CBD is not mediated *via* the 5HT1A receptor.

Hughes, B., Walsh, D., Minnock, and Herron C. (2013), 6th European work shop on cannabinoid research, B.J.Pharm.
Ledgerwood CJ, Greenwood SM, Brett RR, Pratt JA, Bushell TJ. (2011) Br.J.Pharm. 162:286-94.
Hughes, B., Walsh, D., Minnock, and Herron C. (2013) , 6tth European work shop on cannabinoid research. Br.J.Pharm.
Ledgerwood CJ, Greenwood SM, Brett RR, Pratt JA, Bushell TJ. (2011) Br.J.Pharm. 162:286-94.

Poster Ref: P1-F-031

Theme: F: Nervous System Disorders

Xenon provides short term & long term neuroprotection in an *in vivo* model of traumatic brain injury.

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Traumatic brain injury (TBI) is a leading cause of morbidity and mortality in western societies. Despite improvements in medical care, TBI clinical treatment is mainly supportive and no specific neuroprotective drugs are currently available. Over-activation of N-methyl-D-aspartate (NMDA) receptors plays a key role in the spread of injury shortly after TBI. Xenon, a noble gas anaesthetic, is an NMDA receptor antagonist shown to be neuroprotective in models of brain ischemia, and is currently under clinical trial for neonatal asphyxia. Much less is known about xenon effect in the context of brain trauma.

This study focuses on evaluating xenon's neuroprotective potential in a highly reproducible rodent controlled cortical impact model of experimental traumatic brain injury, mimicking elements found after moderate to severe TBI in humans. Adult C57BL/6 male mice (n=196) underwent a right parietal cortical impact under anaesthesia, delivered by a custom-made electro-pneumatic impactor. Animals were randomly assigned into control (75% nitrogen:25% oxygen) and xenon (30%, 50% or 75% xenon:25% oxygen, balanced with nitrogen) treated groups. Short term and long term outcomes, functional and histological, were measured by researchers blinded to treatment.

Our study shows 75% xenon significantly ($p<0.05$) reduced contusion volume 24 hours after injury and significantly ($p<0.05$) improved neurologic outcome score up to 4 days after injury & clinically relevant locomotor parameters 1 month after injury. Xenon treatment significantly ($p<0.05$) reduced contusion volume when given up to 3 hours after injury and significantly ($p<0.05$) improved neurologic outcome when given up to 1 hour after injury. Significant ($p<0.05$) reductions in contusion volume and improvement in neurologic outcome 24 hours after injury were also achieved with 30% and 50% xenon concentrations.

Our results show for the first time that xenon improves functional outcomes and reduces contusion volume in an animal model of TBI. Our findings, including the demonstration of long term neuroprotection and a clinically relevant therapeutic time window, support the idea that xenon may be of benefit as a neuroprotective treatment in TBI patients.

Poster Ref: P1-F-032

Theme: F: Nervous System Disorders

The anxious mind: resting state functional connectivity in generalised anxiety disorder patients and healthy controls.

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Background: Mind wandering, described as a drift away from ongoing activities towards internal thoughts and feelings, is a universal aspect of human cognition. Whenever these thoughts become perseverative, such as during the anticipation of a future threat (*i.e.*, worry), this process becomes maladaptive. Uncontrolled repetitive worry is a main symptom of generalized anxiety disorder (GAD). Using resting state functional magnetic resonance imaging (fMRI), we examined functional connectivity correlates of mind wandering and worry in GAD patients and healthy controls (HC).

Methods: Nineteen GAD patients and 21 HC underwent two 5-min resting state fMRI sessions before and after a worry induction. Probabilistic independent component analysis was used to identify connectivity networks, using MELODIC in FSL (v5). Conn Toolbox v14n (http://www.nitrc.org/projects/conn) was used to asses functional connectivity nodes of candidate networks. The induction, group as well as interaction effects were examined.

Results: Six out of the 11 candidate networks showed main and/or interaction effects. The worry induction led to decreased connectivity in the executive control network, and increased connectivity in the cerebellum hub as well as lateral visual network. The GAD group showed increased functional connectivity in the right and left lateralized fronto-parietal networks, and decreased connectivity in the executive control network. As shown by the Group x Induction significant interactions, connectivity in the medial visual and executive control networks decreased in GAD and increased in HC participants after the induction. This pattern was reversed for the lateral visual networks. Functional connectivity in the cerebellum network increased in both HC and GAD but the increase was significantly larger in HC.

Conclusions: As expected, the transition from adaptive mind wandering to dysfunctional worry is associated with different connectivity patterns in GAD patients and HC.

Poster Ref: P1-F-033

Theme: F: Nervous System Disorders

Heart rate variability predicts neural shift from worrisome thoughts to attentional control in anxious and healthy subjects.

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Excessive worry and difficulty concentrating are hallmarks of anxiety disorder (AD) to the point that they are perceived as uncontrollable and disruptive to patients' everyday life. Based on previous findings suggesting vagal functioning as a marker of cognitive flexibility, we hypothesized that heart rate variability (HRV) would predict the ability of the brain to shift from the spontaneous generation of worrisome thoughts to attentional control. Moreover, we expected this shift to be more problematic in AD compared to healthy participants (HC). Functional magnetic resonance imaging and HRV data were acquired from 19 AD and 21 HC, matched for age (29.3 (8.3) years) and gender, during performance of three low demand tracking tasks. The tasks required participants to visually track a slowly moving circle and press a button as fast as possible to infrequent colour changes of the circle (target events). Randomly, between the second or the third tracking task, all participants underwent a worry induction. Compared to HC, AD participants were characterized by attenuated decreases in brain activity after target events within regions including frontal pole, inferior frontal gyrus, and basal ganglia bilaterally, and left fusiform and lateral temporal cortex. In line with our hypothesis, HRV correlated negatively with this de-activation in key brain regions. Moreover, worry induction differentially impacted brain activity in two groups, particularly affecting the cuneal/precuneus, lateral occipital cortex, and posterior cingulate bilaterally and right superior parietal lobule. In AD, relative to the HC group, the induction had a diminished impact on responses to target presentation. This was consistent with the predicted effects of a higher baseline of worrisome cognitions in AD. Overall, our results increase our understanding of the relationship between anxiety, worry, and impoverished attentional control at both the neural and autonomic level, and help clarify why worry is perceived as more functionally disruptive in patients with AD.

Poster Ref: P1-F-034
Theme: F: Nervous System Disorders

Modulation of intracellular ATP influences seizure activity *via* the activity-dependent release of adenosine.

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University of Warwick

Epilepsy is a debilitating disorder that affects 1% of the UK population, many of whom suffer from epilepsy that is resistant to treatment. Whilst attention has focussed primarily on GABA as the major inhibitory neurotransmitter system targeted in the treatment of epilepsy, the mammalian brain possesses an additional endogenous anticonvulsant – adenosine. As the breakdown product of ATP, the production of adenosine exquisitely reflects the unmet metabolic demands of neurones and acts to limit those demands, for example *via* the inhibition of seizure activity through the activation of adenosine A1 receptors.

Given the importance of intracellular ATP as a reservoir for adenosine we have used rat hippocampal slices to modulate the availability of intracellular ATP and to examine the effects on both extracellular adenosine and seizure activity. Hippocampal slices were pre-treated for 3 hrs with a combination of the sugar backbone of ATP, D-ribose (1 mM) and the purine nucleobase adenine (50 μM; “RibAde”), or creatine (1 mM). We have shown previously that RibAde restores hippocampal slice ATP levels close to those seen *in vivo* (zur Nedden *et al.*, 2011, 2014), and also results in greater activity- and oxygen/glucose deprivation (OGD)-dependent release of adenosine. In contrast, creatine, *via* its conversion to creatine phosphate, acts as a buffer against intracellular ATP breakdown and reduces adenosine release during OGD. In the 0 Mg^{2+}/4-AP model of seizure activity RibAde reduced the frequency and intensity of seizure activity and resulted in greater adenosine release as measured with biosensors (4.1 ± 0.6μM; n = 10) compared to control slices (1.8 μM ± 0.3; n = 10; $p < 0.01$). In contrast, seizure intensity was increased in creatine-treated slices and less adenosine was released in response to seizures (1.3 μM ± 0.3; n = 8; $p < 0.001$).

These studies provide evidence for the beneficial role of the ATP precursors ribose and adenine in reducing seizure activity. Given their prior safe use in humans, RibAde may have value in the treatment of drug-resistant epilepsy.

zur Nedden S. *et al.*, 2011, J. Neuroscience, 31: 6221-34.
zur Nedden S. *et al.*, 2014, J Neurochemistry, 128: 111-24.

Poster Ref: P1-F-035

Theme: F: Nervous System Disorders

Developing a *Drosophila melanogaster* model of traumatic brain injury.

*Alexandra Clifton, *Diya Malhotra, Alessandro Prete, Robert Dickinson and Giorgio Gilestro

Imperial College London

**these authors contributed equally*

Traumatic Brain Injury (TBI) results in a major global healthcare burden and is a leading cause of death and disability in young and elderly populations alike. Following the initial or "primary" injury a series of complex molecular cascades are activated resulting in a delayed or "secondary" injury. Much of the behavioural and cognitive deficits experienced by patients after TBI are due to this secondary injury. The mechanism(s) underlying secondary injury development are not fully understood and current treatments for TBI patients are largely supportive. There is therefore a need for suitable models in which to study the molecular mechanisms underlying secondary injury development. Such models can be used to screen potential therapeutics.

Current *in vivo* models of TBI typically use rodents. These rodent models are costly and also involve ethical issues over animal use. Rapid advances in rodent genetics allow knock-out and knock-in strains to investigate molecular pathways, but at moderate to high cost. A *Drosophila* model offers a novel solution, eliminating use of rodents, and is inexpensive. Key advantages include: high throughput and inexpensive assays to establish causality between injury severity, outcomes and treatments, the opportunity to conduct whole-lifetime studies and an array of molecular and genetic tools which may be used to isolate pathways in injury development. *Drosophila melanogaster* has provided useful insights into neurodegenerative disorders and therefore similar strategies may be applied in traumatic brain injury.

We are developing a *Drosophila* model of TBI, which uses a mechanically controlled impactor to produce a concussion-like injury. The survival of flies after injury is quantified over a fixed time period. The advantages of our model include reproducibility and control of injury severity. Our data shows that survival in the 14 days after trauma depends on the severity of the injury (number of impacts) and that there is a steady decline in survival after day 5 onwards in flies that received 5 strikes and a slower decline in those that received 1 strike. We will use this model to investigate the pathways involved in injury development and to investigate the neuroprotective potential of novel treatments.

Poster Ref: P1-F-036

Theme: F: Nervous System Disorders

The neuroprotective efficacy of noble gases in an *in vitro* model of ischemic brain injury.

Mariia Koziakova, Katie Harris, Rita Campos-Pires, Diya Malhotra, Nicholas Franks and Robert Dickinson
Imperial College London

The inert anesthetic gas xenon is neuroprotective in models of ischemic and traumatic brain injury and xenon is undergoing clinical trials as a treatment for neonatal asphyxia and brain damage after cardiac arrest. Here we investigate the neuroprotective efficacy and mechanism of action of the inert gases xenon, argon, krypton, neon and helium in an *in vitro* model of ischemic brain injury.

We use an *in vitro* model of ischemic brain injury using organotypic hippocampal brain-slices from mice, subjected to oxygen-glucose deprivation (OGD).

We show that 50% atm xenon and 50% argon are neuroprotective against ischemic injury when applied following injury. The other inert gases, helium, neon and krypton are devoid of neuroprotective effect. We show that adding glycine reverses the neuroprotective effect of xenon, consistent with competitive inhibition at the NMDA receptor glycine-site mediating xenon neuroprotection against traumatic brain injury. Argon neuroprotection is not reversed by glycine, indicating that argon does not act at the NMDA receptor glycine site.

Xenon neuroprotection against ischemic brain injury can be reversed by elevating the glycine concentration, consistent with competitive inhibition by xenon at the NMDA-receptor glycine site playing a significant role in xenon neuroprotection. Argon does not act *via* the same mechanism as xenon.

Poster Ref: P1-F-037

Theme: F: Nervous System Disorders

Methylthioninium administered in either oxidised or reduced form attenuates motor impairments in tau transgenic mice.

Valeria Melis, Pierre-Henri Moreau, Charles R. Harrington, Claude M. Wischik and Gernot Riedel
University of Aberdeen

Intracellular accumulation of filamentous tau deposits are neuropathological hallmarks of more than 30 neurodegenerative disorders, collectively named tauopathies, which are associated with the progressive loss of cognitive, behavioural and motor functions. The most common tauopathy is Alzheimer's disease (AD), but tau inclusions are also shared in frontotemporal dementias (FTDP-17) and progressive supranuclear palsy (PSP).

The strong correlation between neurofibrillary pathology and clinical decline in tauopathies supports the increasing interest in novel therapeutic strategies aimed to prevent and inhibit accumulation of tau aggregates.

Transgenic mouse models displaying progressive deterioration of motor functions similar to that found in FTDP-17 have proven to be highly valuable for the development of such therapeutic strategies. This study investigated the effect of two tau-aggregation inhibitors (TAIs) in a novel mouse model, termed Line 66, which expresses the full-length human tau isoform containing the P301S and G335D mutations (Melis *et al.*, 2014, CMLS in press). Line 66 mice are characterized by severe neurofibrillary pathology associated with a prominent motor phenotype, as revealed in the RotaRod test.

The efficacy of methylthioninium (MT) administered either as a chloride salt (MTC) or in a reduced form (LMTX®) was compared in 8-9 months old Line 66 mice. Animals were orally treated for 19 consecutive days and motor performance re-assessed in the RotaRod task.

Administration of MT in either oxidized or reduced form ameliorated the motor impairment in transgenic mice and had no effect on wild-type controls. Although both drugs produced comparable benefit in Line 66 mice, a relative superiority of LMTX® compared to MTC was detected, likely due to a difference in absorption, metabolism and distribution. All these findings, along with phase 2 clinical trial results, validate the rationale for the use of tau aggregation inhibitors for the treatment of AD and neurodegenerative tauopathies.

Poster Ref: P1-F-038

Theme: F: Nervous System Disorders

Behavioural characterization of tau transgenic mouse lines modelling taupathies: Alzheimer and FTD phenotypes.

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[1]School of Medicine and Dentistry, University of Aberdeen, [2]University of Aberdeen, [3]School of Medical Sciences.

Nowadays tauopathies remains poorly understood because of their different clinical symptoms. Alzheimer's disease (AD) is well characterized by a progressive and age-related cognitive decline whereas Frontotemporal Dementia (FTD) is dominated by motor and emotional/psychiatric abnormalities. Moreover, genetic mutations are only confirmed for FTD, but not for AD. This observation suggests that different genetic mouse lines could mimic different forms of tauopathies.

The current study aimed to investigate new tau transgenic lines in multiple tasks that interrogate core-features of tau-related dementias (cognition, anxiety, anhedonia, olfaction and depression). Here, we compared NMRI-derived mice overexpressing different human tau protein constructs both under the control of a neuron-specific Thy-1 promoter. Line 1 mice express a truncated form of the human tau gene corresponding to residues 296-390 whereas Line 66 contains the full-length human Tau isoform carrying a double mutation P301S/G335D (Melis *et al.*, 2014, CMLS in press). Behavioural results were dependent on gene construct. Relative to controls expressing high preference for novel objects/social partners rather than familiar ones, Line 1 mice had no recognition bias and Line 66 showed signs of neophobia by preferring familiar objects. In addition, anxiety and sucrose preference was lower only in Line 66 mice and no sign of olfactory deficit was found between groups.

In line with our previous findings, these results tend to confirm that L66 mice models symptoms observed in FTD whereas L1 showed deficits consistent with AD.

Poster Ref: P1-F-039

Theme: F: Nervous System Disorders

Effects of NMDAR antagonists and antipsychotic drugs on high frequency oscillations recorded in the nucleus accumbens of freely moving mice.

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The nucleus accumbens (NAc) is a brain region that has been implicated widely in the pathophysiology of schizophrenia and the NMDA hypofunction model of schizophrenia. Consistent with our finding from rats, NMDAR antagonists dose-dependently increased the power of HFO and produced small increases in their frequency in mice. The atypical antipsychotic drug, clozapine, dose-dependently reduced the frequency of HFO, whilst haloperidol a typical antipsychotic drug had little effect. Atypical antipsychotics target many different receptor types and we investigated the mechanism underlying clozapine-induced reductions in HFO frequency using a pharmacological strategy. We found systemic administration of glycine reduced the frequency of HFO to levels comparable to clozapine. Systemic injection of NMDA produced a short-lasting reduction in HFO frequency. Further, clozapine-induced reductions in HFO frequency were reversed by a high dose of MK801. Other receptors, known to be targets for atypical antipsychotics, namely 5HT-2A, -1A, -7 and histamine 3 receptors did not appear to underlie antipsychotic-induced reductions in HFO frequency. These findings show that: (1) the fundamental effects produced by NMDAR antagonists/antipsychotics on HFO in the NAc of mice and rats are broadly similar and (2), NMDAR are involved in the mechanism underlying reduction in HFO frequency produced by antipsychotic drugs.

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Poster Ref: P1-F-040

Theme: F: Nervous System Disorders

Characterisation of a neural stem cell population isolated from adult mouse cerebellum.

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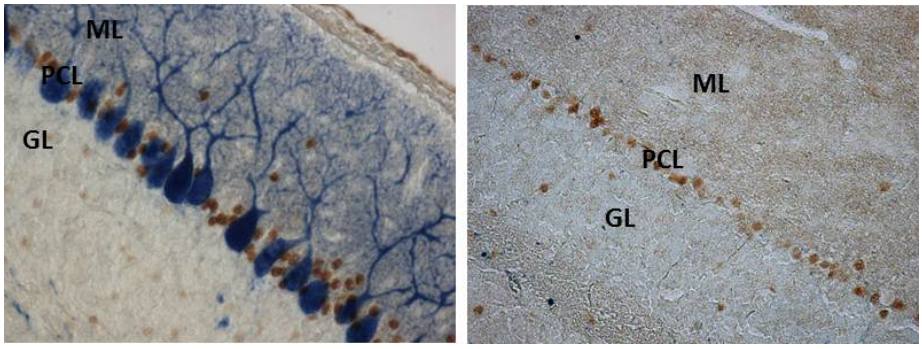
In mammals, adult neurogenesis is thought to be restricted to two regions in the brain, the lateral ventricle and the hippocampus. Recently, cells exhibiting some stem cell characteristics have been isolated from the adult cerebellum in mice. These cells have been identified in the adult mouse and human as the Bergmann glia, the radial glia in the cerebellar cortex characterised by long radial processes extending to the pial surface. Bergmann glia cells exhibit expression of neural stem cell (NSC) markers such as Sox1, Sox2, and Sox9. We further set out to determine the wider expression profile of this population for NSC markers, as well as markers associated with NSCs in adult mouse, chick, and non-human primate cerebella. Immunohistochemical analysis confirms that the cerebellum in the these species harbours a population of cells located in the Purkinje cell layer expressing Sox1, Sox2, and Sox9 and several markers associated with NSCs. Furthermore, we show that the adult mouse cerebellum contains neural stem cells that show stem cell characteristics and have the capacity for proliferation and differentiation into different cell lines such as neurons and astrocytes. The isolated cells express various NSCs and radial glial markers, matching our results in the adult mouse cerebellar tissue. The present study demonstrates that stem cells can be isolated from adult cerebellum which might have an important implication to evaluate a novel therapeutic approach for cerebellar tissue repair.



Poster Ref: P1-F-041

Theme: F: Nervous System Disorders

Analysing Trappc9 functions *in vitro* and in a mouse model of autosomal non-syndromic intellectual disability.

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Homozygous mutations in the gene for Trafficking Protein Particle Complex 9 (Trappc9) have been associated with autosomal non-syndromic intellectual disability. Cognitive impairment, incapability of speech, microcephaly and thinning of the corpus callosum are predominant features among the patients diagnosed with this condition. These symptoms, which become apparent from early childhood, indicate an important function of Trappc9 during brain development.

However, little is known about the molecular functions of Trappc9. This protein has been described as a part of the multi-protein complex TrappII involved in Golgi vesicle trafficking, and it can promote gene expression *via* regulation of the NF-kB pathway (*via* NIK, IKKβ, IkBα, p65). It also interacts with the p150Glued subunit of dynactin suggesting a possible role in retrograde transport along microtubuli. Interestingly, the presence of Trappc9 is essential for the NFG-induced neurite outgrowth in PC12 cells. Trappc9 might, therefore, impact on brain development *via* regulating neurite extension and/or response to trophic factors and cytoskeleton organisation.

Using immunohistochemistry, we found Trappc9 to be expressed in a subset of scattered neurons in most brain regions. A partial co-localisation with the anti-apoptotic factor Bcl-xl suggests a possible role in cell survival.

We established two stable Neuro2A cell lines with >70% knock-down of Trappc9 using Lentivirus shRNA vectors. Currently, we are in the process of analysing neurite formation, proliferation and NF-kB activation in these cells. Furthermore, we have constructed a vector encoding for a GFP-Trappc9 fusion protein to study its intracellular localisation and involvement in transport processes.

We also investigated potential Trappc9 transcript variants in mouse postnatal brain samples, and in contrast to the published ENSEMBL data we did not find any evidence for an alternative start exon, alternative splicing or for truncated transcripts.

We have also established a conditionally targeted “floxed” Trappc9 mouse line and we are currently undertaking crosses with Nestin-Cre mice for brain specific deletions, in order to recapitulate the human disorder and to study the role of Trappc9 in brain development.

Poster Ref: P1-F-042

Theme: F: Nervous System Disorders

3-Iodothyronamine rescues β-amyloid-dependent long term potentiation impairment in the entorhinal cortex.

Alice Accorroni[1], Chiara Criscuolo[2], Martina Sabatini[3], Riccardo Donzelli[3], Alessandro Saba[3], Riccardo Zucchi[3] and Nicola Origlia[2]

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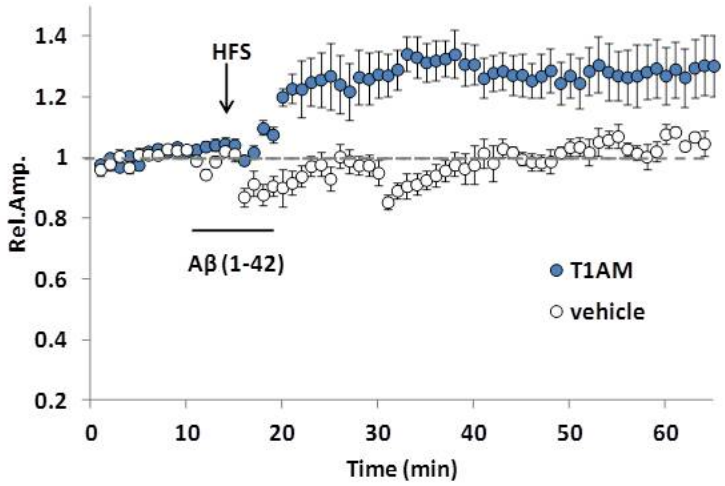
Beta-amyloid (Aβ) is the principal component of senile plaques, which represent a prominent pathological feature of Alzheimer's disease (AD) and influence its well-characterized cognitive symptoms. However, loss of neuronal function and cognitive impairment in AD patients precede the formation of Aβ plaques. We have previously reported that soluble Aβ oligomers impair synaptic transmission and plasticity in the entorhinal cortex (EC), an area crucially involved in cognitive functions and affected in AD at a very early stage. Recently, 3-iodothyronamine (T1AM), a novel endogenous amine, was shown to stimulate memory acquisition in the mouse.

Our aim was to investigate whether T1AM could exert a protective effect in the Aβ-induced impairment of synaptic plasticity.

Synaptic function was studied recording extracellular field potentials evoked in cortical layers II–III of entorhinal cortex slices. Long term potentiation (LTP) was elicited by high frequency stimulation.

We first evaluated the effects of T1AM perfusion alone on EC slices from wild-type mice, and identified a concentration (5 μM) that did not affect either basal synaptic transmission or LTP induction and maintenance. As previously reported, Aβ oligomeric peptide at a concentration of 200 nM inhibits LTP without affecting basic synaptic transmission. T1AM perfusion before the delivery of high frequency stimulation was able to rescue LTP in Aβ-treated slices. The protective effect of T1AM was also confirmed in slices from transgenic AD mice (mhAPP-J20), which show LTP impairment in the EC at a very early stage (2 months). Furthermore, endogenous T1AM concentration, measured in the EC of mhAPP-J20 by high-performance liquid chromatography coupled to mass spectrometry, was slightly reduced when compared to control wild-type littermate.

Our results highlight the possible neuroprotective role of T1AM, an endogenous thyroid hormone relative which is particularly concentrated in brain tissue. A more thorough understanding of the neuroprotective properties of T1AM and the underlying mechanisms of its effect on Aβ-induced neuronal dysfunction, may be beneficial for clinical research and would lead to the identification of new pharmacological targets to delay disease progression.



The administration of oligomeric Aβ peptide at a concentration of 200 nM inhibits long term potentiation (LTP) in EC slices. As it can be seen in the figure, T1AM administration before high frequency stimulation delivery rescues LTP in slices treated with oligomeric Aβ peptide.

Poster Ref: P1-F-043

Theme: F: Nervous System Disorders

Alcohol consumption in young adults: the role of psychological factors.

James King, Lucinda Doyle, Mark Tarrant and Crawford Winlove

University of Exeter Medical School

Aim: Patterns of behaviour that develop in early-adulthood may have long-lasting effects on subsequent behaviour. This has important implications for alcohol consumption and the incidence of subsequent addiction. It is striking that few recent studies have saught to establish whether high levels of alcohol consumption continue to occur in young adults in the UK. We have addressed this gap in the evidence, and started to explore the factors that could underlie these patterns of alcohol consumption.

Method: We recruited undergraduate participants from our host institution, and from further afield using social media. Participants completed surveys at two points in a the first half of December, with the intention that this would allow us to explore whether participants have different salient identities depending on their immediate environment. The questionnaires included the following validated measures: 1) the Alcohol Use Disorders Identification Test Consumption (AUDIT-C), a measure of alcohol consumption; 2) the Modified Drinking Motives Questionnaire-Revised (DMQ-R), a measure of the motivations underlying drinking behaviours; 3) the Barratt Impulsiveness Scale (BIS), a measure of trait impulsiveness.

Results: 172 participants completed the survey at the time of writing; the surveys remain open, so the number of participants should continue to increase. Participants in our survey drink in excess of Government guidelines, and many show hazardous binging behaviour. Preliminary analyses suggest that the rate at which these behaviours occur are significantly higher than that seen in the wider UK population, and in student populations in other countries. Work is underway to explore the relationship between drinking patterns and the roles of anxiety and social conformity. Finally, we will report the role of trait impulsivity in the motivations and drinking habits of our participants.

Conclusion: We report that levels of alcohol consumption are indeed high amongst young-adults. Consumption is highest amongst individuals that also show high levels of anxiety or impulsivity. This has important implications for understanding risk factors in addiction.

Poster Ref: P1-F-044

Theme: F: Nervous System Disorders

The neuroimaging of addiction: functional and structural changes associated with opiates and psychostimulants.

James Whitfield, Coco Chan, Joe Yates and Crawford Winlove

University of Exeter Medical School

Aim: We used co-ordinate-based meta-analyses to explore how opiate and psychostimulant addiction affect cue-reactivity and brain structure.

Method: We systematically searched the Web of Knowledge, PubMed, Embase, PsycINFO, and CINAHL. Data from papers that satisfied our a priori selection criteria were subject to calculations using Activation Likelihood Estimation (ALE, Eickhoff, 2009, implemented in GingerALE, v2.1.1), Multi-level Kernel Density Analysis (MKDA, Xie, Li *et al.* 2011) and Signed Differential Mapping (SDM, Li *et al.* 2008).

Results: ALE revealed 13 statistically significant regions in which activation was greater for heroin-related cues than neutral cues, the largest of which were BA37 (48,−66,-4; 1776mm^3), thalamus (2,−14,4; 1656mm^3), and amygdala (−22,−4,−16; 1296mm^3). There were pronounced differences in activation between short-term (ST) and long-term (LT) abstinent opiate addicts (short-term, 24.5 ± 20.0 days; long-term, 229.5 ± 82.2 days). In the ST (187 foci) there were significant activations in nine regions, the largest being caudate (−6,12,0; 1448mm^3), amygdala (−22,−4,−16; 1432mm^3) and thalamus (0,−12,4; 1320mm^3). The LT (74 foci) had five regions of significant activation, the most notable of which was extensive bilateral BA37 (−48,−68,2; 928mm^3; 46,−66,−2; 1032mm^3; 48,−52,-10; 280mm^3). In contrast, the analysis of these data using MKDA revealed just four regions in which the contrast of heroin-related cues to neutral cues reached statistical significance, whilst SDM revealed five regions. The analysis of the structural data for opiate users identified a single region in the frontal gyrus. The analysis of our psychostimulant data is ongoing.

Conclusion: The cue-reactivity data suggest that treatment efficacies could be evaluated by comparing temporal changes in activation over the course of sustained abstinence. It is striking that opiate and psychostimulant abuse are not associated with extensive structural changes. The observation that conceptually similar algorithms yield substantively different results raises some important questions.

Poster Ref: P1-F-045
Theme: F: Nervous System Disorders

The neuropsychological profile of psychostimulant abuse: a meta-analysis.

Katie Simms and Crawford Winlove
University of Exeter Medical School

Aim: We used meta-analyses to characterise the neuropsychological impact of psychostimulant abuse. This is a first-step towards identifying distinctive sub-groups within larger populations.

Method: We systematically searched the Web of Knowledge suite and PubMed database, using the Taporware text analytics tool to optimise these searches. Our final search of MEDLINE used the following algorithm: ((Psychostimulant[Title] OR cocaine[Title] OR amphetamine[Title] OR methamphetamine[Title])) AND (cognit*[Title] OR impair*[Title] OR function[Title] OR assessment[Title] OR effects[Title] OR treatment[Title] OR performance[Title] OR neuropsychological[Title] OR task[Title] OR test[Title] OR deficit[Title]). The papers identified that satisfied our inclusion criteria were assigned to one of the following eight cognitive domains: Executive Function, Attention, Memory, Learning, Speed of Processing, Language, Motor function, inhibition/Impulsivity.

Results: Our search identified a total of 8047 papers on the 5th November 2014. Papers were removed from this sample if they did not study humans (5327), were not written in English (96), or were not one of the following: a journal article, case-report, clinical trial, letter, meta-analysis, review, systematic review, or a randomised-controlled trial (19). Both authors read the abstract of the remaining 2605 papers to establish their suitably on the basis of our a priori criteria. This identified a final sample of 147 papers. Most of these papers examined neuropsychological performance following abstinence for short periods (<6 months) or long periods (>6 months). Our calculations of effect sizes for these data are currently underway using Stata 13.

Conclusion: Our preliminary calculations suggest that there is moderate impairment across most cognitive domains during the early stages of psychostimulant abstinence. Over longer periods some impairment remains, but the effect size is very small. This presents an encouraging picture for those recovering from addiction, though it remains to be established whether those with a long history of recurring relapse have more severe impairments.

Poster Ref: P1-F-046

Theme: F: Nervous System Disorders

Imaging imagination: an activation likelihood estimation (ALE) meta-analysis.

Jake Ranson, Alexander Clunies-Ross, Crawford Winlove and Adam Zeman

University of Exeter Medical School

Aim: We conducted a co-ordinate-based meta-analysis of published fMRI data to identify regions of the brain which are consistently activated during visual imagination.

Method: We systematically searched the Web of Knowledge, PubMed, Embase, PsycINFO, and CINAHL; search terms were optimised using Taporware (Text Analysis Portal for Research). Data from papers satisfying our a priori selection criteria were subject to calculations using Activation Likelihood Estimation (ALE, Eickhoff, 2009, implemented in GingerALE, v2.3.2).

Results: The searches identified a total of 4069 papers on the 29th October 2013. Papers were removed from this sample if they did not study humans (224), were not written in English (350), or were not one of the following: an article, review, meta-analysis, case report, letter, abstract or clinical trial (270). Of the remaining articles, 1118 were duplicates and were therefore removed. The authors read the abstract of the remaining 2107 papers to establish their suitably on the basis of our a priori criteria. Ultimately, we found 14 papers suitable for inclusion, with a total of 255 foci.Using an FDR of 0.05 and a minimum cluster volume of 120 mm^3 the calculations identified 23 clusters of consistent activation. The largest activations were in the precuneus and superior parietal lobule (2720 mm^3), the fusiform gyrus (2424 mm^3) and the inferior frontal gyrus (1792 mm^3). Activations in the fusiform gyrus and the inferior frontal gyrus remained when calculations were performed on the sub-set of studies in which participants were instructed to close their eyes, but were absent when participants had their eyes open. Work is underway to compare aural and visual cues.

Conclusion: Visual imagery activates a consistent set of brain regions, and these overlap substantially with the set of regions which are active during perception. Imagery-related activations are stronger when perception is suppressed.

Poster Ref: P1-F-047

Theme: F: Nervous System Disorders

Deciphering transcriptional regulation at the schizophrenia-associated miR-137 locus.

Olympia Gianfrancesco, Maurizio Manca, Alix Warburton, Daniel Griffiths, Vivien Bubb and John P Quinn
University of Liverpool, Liverpool

Background: Recent schizophrenia genome-wide association studies have identified 2 highly associated SNPs (rs1625579 and rs1198588) at the miR-137 locus, revealing this region to be among the strongest findings for association with schizophrenia. As neither of these are exonic SNPs, the onset of schizophrenia associated with these SNPs is likely linked to environmental factors. Identifying key DNA regulatory regions of miR-137 expression is crucial to understanding the transcriptional control and environmental response of miR-137 that might underpin schizophrenia.

Results: Through alignment and comparison of multiple vertebrate genomes, we have identified non-coding regions at the miR-137 locus with conservation comparable to that of exons (70+%), thereby indicating potential functional significance. 8 of the 9 evolutionary conserved regions (ECRs) studied support significant changes in reporter gene expression in the SH-SY5Y neuroblastoma cell line. Furthermore, linkage analysis revealed 2 of these ECRs to be in strong linkage disequilibrium with the 2 schizophrenia GWAS SNPs and a novel promoter at this locus, thereby suggesting functional significance of these conserved regions in the expression of transcripts from this promoter and, more broadly, in the aetiology of schizophrenia. In addition, this study demonstrated that both schizophrenia GWAS SNPs are associated with a novel, brain-expressed RNA at this locus, with potential relevance to psychiatric disorders.

Conclusion: Bioinformatics and reporter gene constructs have been used to identify and characterise 9 highly conserved non-coding regions at the schizophrenia-associated miR-137 locus. We demonstrate the transcriptional regulatory activity of these ECRs, highlight strong linkage disequilibrium between the miR-137 schizophrenia SNPs and 2 of the ECRs studied, and identify a novel, brain expressed RNA. This suggests a functional role for the ECRs in the regulation of these RNAs, and highlights a potential role for the novel RNA in the molecular underpinnings of psychiatric disease.

Poster Ref: P1-F-048

Theme: F: Nervous System Disorders

Neurotrophin-3 modulates spinal reflexes after central nervous system injury.

Claudia Kathe, Stephen McMahon and Lawrence Moon

Wolfson CARD, King's College London

Neurotrophin-3 (NT3) promotes the survival and neurite extension of specific neuronal populations including Ia proprioceptive fibers. We will investigate the mechanism by which NT3 modulates spinal reflexes mediated *via* this neuronal population and motor neurons *in vivo*.

Firstly, we evaluated retrograde trafficking of NT-3 towards the spinal cord following AAV-NT3 overexpression in forelimb muscles. We have detected increased levels of NT3 protein in dorsal root ganglia connecting to the treated muscle groups.

Secondly, we use electrophysiology to functionally test the effects of NT3 overexpression in the muscle on the modulation of spinal reflexes involving proprioceptors and motor neurons. Rodents, like humans, develop spasticity after spinal cord injury or stroke, caused by the hyper-excitability of the spinal reflex pathway. Thus, we developed an animal model, which allows for repeated electrophysiological assessment of this monosynaptic reflex. More specifically, we recorded the H-reflex from the abductor digiti quinti, a forepaw muscle, in rats every two weeks up to 10 weeks after a bilateral pyramidotomy. Rats were treated 24 hours post-injury by injection of an AAV-NT3 (or AAV-EGFP as a control treatment) into the forelimb flexor muscles on one side. Naive animals show a frequency-dependent depression of the H-wave at higher stimulation frequencies. After injury, this effect is reduced. However, one group recovers to baseline levels after 6 weeks post-injury whereas the other does not. We will evaluate motor movement in the forelimb with a number of behavioural tests and determine if it correlates with these electrophysiological changes. Furthermore, we will dissect out how proprioceptors and motor neurons respond to NT3 treatment by stimulating and recording from antagonistic nerves in the forelimb. After analysis treatment allocations will be unblinded.

Due to the clinically relevant delivery method and profound effects observed after spinal cord injury following NT3 treatment, our data will show whether spinal reflexes can be positively modulated after CNS injury.

Poster Ref: P1-F-049

Theme: F: Nervous System Disorders

Laser microdissection of *in vivo* regenerating spinal neurons identifies genes including Ptpn2 that promote axon sprouting and sensorimotor recovery after CNS injury.

Thomas Hutson[1], Lawrence Moon[1], Claudia Kathe[1], Ronald van Kesteren[2], Jorge Torres-Muñoz[3], Carol Petito[3], Christopher Bowen[4], James Aimone[5], William Buchser[4], Vance Lemmon[4], John Bixby[4], August Smit[2], Fred Gage[5] and Mary Bunge[4]

[1]Wolfson Centre for Age-Related Diseases, King's College London, [2]Center for Neurogenomics and Cognitive Research, VU University, Amsterdam, The Netherlands, [3]Department of Pathology, University of Miami, FL, USA, [4]The Miami Project to Cure Paralysis, University of Miami, FL, USA, [5]The Salk Institute for Biological Studies, La Jolla, CA, USA

Following injury to the central nervous system (CNS), neurons show a very limited axonal regenerative response due to a reduced intrinsic growth state and the presence of growth inhibitory molecules that form a molecular and physical barrier to regeneration. Our aim is to enhance the intrinsic growth state of CNS neurons by over-expressing genes that enhance regeneration, enabling neurons to overcome the growth-inhibitory environment and increase axon regeneration. To identify novel targets for spinal cord repair, a novel strategy was used to identify genes that promote CNS axon regeneration. We laser microdissected spinal neurons that regenerated axons into a Schwann cell bridge implanted following complete transection of the adult rat cord. Microarray comparison of mRNAs from sprouting *vs*. non-sprouting neurons identified 552 known and novel regeneration-associated genes (RAGs). Functional screening of >500 RAGs using a medium-throughput electroporation assay showed that over-expression of Ptpn2 increased the neurite outgrowth of CNS neurons on two different growth-inhibitory substrates *in vitro*. Furthermore we developed bicistronic AAV vectors that over-express Ptpn2-2A-eGFP and tested these in a pyramidotomy model of CNS injury. AAV-mediated over-expression of Ptpn2 in the motor cortex resulted in enhanced midline sprouting of the treated, un-injured corticospinal axons, leading to significant electrophysiological and behavioural improvements. In addition, we demonstrate that the mechanism by which Ptpn2 increases neurite outgrowth and axon regeneration requires the nuclear localisation signal and the DNA binding domain rather than the phosphatase domain. Ptpn2 is a novel potential target for promoting axon sprouting after spinal cord injury.

Poster Ref: P1-F-050

Theme: F: Nervous System Disorders

Epigenome-wide analysis of methylation in a family with a balanced t(1;11) translocation co-segregating with major mental illness.

Daniel McCartney[1], Rosie M. Walker[1], Douglas H. Blackwood[1], J. Kirsty Millar[1], Pippa A. Thomson[1], W. Richard McCombie[2], David J. Porteous[1] and Kathryn L. Evans[1]

[1]University of Edinburgh, [2]Stanley Institute for Cognitive Genomics, Cold Spring Harbor, USA

Background: Recent genome-wide studies have implicated aberrant patterns of DNA methylation as a biomarker in psychiatric illness. Here, we present our findings of differential DNA methylation in an extended Scottish pedigree with a balanced translocation t(1;11)(q42;q14.3) previously shown to be linked to major mental illness.

Methods: Genome-wide methylation was profiled in DNA derived from whole blood in 17 translocation carriers and 24 non-carrying relatives using the Illumina Infinium HumanMethylation450 BeadChip array. Raw data were pre-processed, normalised and analysed in R. Significantly differentially methylated loci were identified by linear regression, fitting age, gender and significant surrogate variables as covariates.

Results: Analysis of individual CpG loci identified significantly differentially methylated positions (DMPs) flanking the t(1;11) breakpoint. All 12 of the most significant DMPs (FDR $q \leq 0.05$) were on the translocation-affected chromosomes. The most distal of these sites were approximately 10Mb and 31Mb from the breakpoints of chromosomes 1 and 11 respectively. Four of these DMPs were within DISC1, a candidate risk gene for psychiatric illness, which is directly affected by the translocation. Analysis of differentially methylated regions (DMRs) also identified a number of loci beyond chromosomes 1 and 11.

Discussion: Our DMP results suggest that the t(1;11) translocation has a relatively long-range effect on chromatin structure extending from the translocation breakpoint. We have also identified regions of differential methylation between t(1;11) carriers and non-carriers outwith the translocated chromosomes. Future work will include validation of these findings along with methylation and expression analyses in family-derived iPS material.

Poster Ref: P1-F-051

Theme: F: Nervous System Disorders

Divisive inhibition prevents abrupt transition from order to chaos in a neural mass model.

Christoforos Papasavvas, Yujiang Wang, Andrew Trevelyan and Marcus Kaiser
Newcastle University

Experimental results suggest that there are two distinct mechanisms of inhibition in cortical networks: subtractive and divisive inhibition. Subtractive inhibition shifts the neuronal input-output function to the right without changing the slope, whereas divisive inhibition causes a reduction in slope or the maximal firing rate. Notably, recent experiments done using optogenetics show that these mechanisms are delivered by different populations of interneurons with a well understood connectivity between them and the pyramidal population. While most research has focussed on understanding the gain control, the role of these inhibitory mechanisms in regulating the dynamics of the network is less well understood. This work presents a novel mathematical model of this basic neocortical circuitry, which incorporates the two inhibitory mechanisms. We investigated the role of these inhibitory mechanisms in terms of network dynamics, and particularly focussing on the transition from ordered to chaotic behaviour. We show that the model incorporating divisive inhibition exhibits quite different behaviour compared to an equivalent model without divisive inhibition. The presence of divisive inhibition in the network prevents the abrupt transition from regular to chaotic dynamics across the parameter space. In contrast, in models which only have subtractive inhibitory elements, there are many cases where small changes in synaptic strength result in sudden flips from stable to chaotic network behaviour. Synaptic plasticity has been postulated as a mechanism by which the brain learns and stores information. Our results have interesting implications, therefore, for how such plastic changes impact on the stability of dynamic network activity patterns. It is also relevant to other network transition such as from physiological to pathological (epileptic) brain dynamics.

Poster Ref: P1-F-052

Theme: F: Nervous System Disorders

Investigating auditory event-related potentials and mismatch negativity-*like* responses in the schizophrenia-related *Map2k7* gene disruption model.

Jamie O'Reilly[1], Rebecca Openshaw[2], Mark Thomson[3], Shuzo Sakata[3], John Dempster[3], Brian Morris[2], Bernard Conway[1] and Judith Pratt[3]

[1]Department of Biomedical Engineering, University of Strathclyde, [2]Institute of Neuroscience and Psychology, Glasgow University, [3]Strathclyde Institute of Pharmacy and Biomedical Science

Mismatch negativity (MMN) responses in patients with schizophrenia (SCZ) typically have lower peak amplitudes than healthy age-matched controls, suggested to reflect abnormal *N*-methyl-D-aspartate (NMDA) receptor mediated signalling. Numerous polymorphisms linked to SCZ impact cellular machinery operating at the glutamatergic synapse. Understanding how these contribute to neuropathology and concurrent electrophysiological changes which occur will enable clinicians to interpret MMN as a biomarker of SCZ.

In this study we utilise a genetically altered mouse model to investigate the role of *MAP2K7*, an intracellular signalling kinase activated in post-synaptic neurons by glutamate binding to NMDA receptors. Using this model we explore the influence of *Map2k7* gene disruption on the generation of auditory evoked potentials (AEPs) and MMN-*like* responses relevant to SCZ. Seven heterozygous (*Map2k7*$^{+/-}$) and ten wild-type (*Map2k7*$^{+/+}$) mice were anaesthetised with urethane and implanted bilaterally with recording electrodes above the primary auditory cortex and a single ground electrode above the cerebellum. Cortical EEG was recorded during various auditory stimulation sequences including the oddball paradigm used to generate MMN-*like* activity, deviant-alone and many-standards control protocols, with deviant stimuli varying in duration, frequency and intensity in the presence and absence of the non-selective NMDA receptor antagonist ketamine.

Results obtained indicate that disruption of the *Map2k7* gene influences cortical auditory processing electrophysiology, with heterozygous mice demonstrating significantly increased stimulus onset and offset AEP amplitudes than their wild-type counterparts. Both frequency- and intensity-deviant oddball stimuli elicited MMN-*like* activity post stimulus offset. These MMN-*like* peak amplitudes were reduced in *Map2k7*$^{+/-}$ mice and by administering ketamine, however each by separate mechanisms. Overall, this provides evidence that MMN-*like* responses are abnormal in *Map2k7*$^{+/-}$ mice, suggesting a phenotype relevant to SCZ.

This research was supported by the EPSRC CDT in Medical Devices and Healthcare Technologies.

Poster Ref: P1-F-053

Theme: F: Nervous System Disorders

Early dysfunction and non-cell autonomous disease mechanisms in a human iPSC- based model of ALS.

Anna-Claire Devlin[1,2], Chen Zhao[2], Karen Burr[2], Siddharthan Chandran[2] and Gareth Miles[1,2]

[1]School of Psychology and Neuroscience, University of St. Andrews, [2]Euan MacDonald Centre for Motor Neurone Disease Research, University of Edinburgh

Amyotrophic Lateral Sclerosis (ALS) is a devastating neurodegenerative disease which remains largely untreatable and incurable, reflecting an incomplete understanding of the key pathogenic mechanisms which underlie motor neuron (MN) loss in the disease. Through the use of induced pluripotent stem cells (iPSCs), we can now study cells from the human central nervous system at a range of time points, including those prior to overt pathology, in order to understand early causative events in ALS. In this study, we report the use of human induced pluripotent stem cell (iPSC)-derived MNs to study the pathophysiology of ALS. We have utilised whole-cell patch clamp recording techniques to investigate whether the functional properties of human iPSC-derived MNs are altered in cells derived from ALS patients compared to healthy controls. We have demonstrated that patient iPSC-derived MNs harbouring C9ORF72 or TARDBP mutations, display an initial hyperexcitability followed by progressive loss of action potential output due to a decrease in voltage-activated Na^+ and K^+ currents which occurs in the absence of changes in cell viability. Given evidence supporting non-cell autonomous disease mechanisms in ALS, we are currently studying whether interactions between neurons and astrocytes are involved in the pathophysiological phenotype we have recently revealed. Preliminary data suggest that patient iPSC-derived astrocytes can induce pathophysiological changes in controls human iPSC-derived MNs which are similar to those we have recently revealed in patient iPSC-derived MNs. We are currently investigating if such non-cell autonomous mechanisms are common across C9ORF72 and TARDBP lines and whether they rely on direct astrocyte-MN interactions. Overall, our data implicate MN dysfunction, potentially due to non-cell autonomous disease mechanisms, as an early contributor to downstream degenerative pathways that ultimately lead to MN loss in ALS.

Poster Ref: P1-F-054

Theme: F: Nervous System Disorders

Expression of TREM receptors in the brain is modified by experimental stroke, showing contrasting temporal profiles and differential contributions of myeloid cell subpopulations.

Alessio Alfieri, Claire Davies, Laura McCulloch and Barry McColl

The Roslin Institute, University of Edinburgh

Neuroinflammation is a major event in the pathophysiology of ischaemic stroke and is largely orchestrated by brain resident and invading myeloid cells. Triggering receptors expressed on myeloid cells (TREMs) are a class of surface receptors involved in myeloid cell activation and phagocytosis. Although TREM1 enhances inflammation, while TREM2 has been shown to function as a negative regulator, their role in cerebral ischaemia is unclear.

Aim of our study was to investigate the temporal profile and cellular origins of TREM receptors in the brain after experimental stroke, together with established markers of neuroinflammation. Mice were subjected to transient intraluminal middle cerebral artery occlusion (MCAO), followed by 1 to 14 days of reperfusion. Transcription and protein expression of TREMs in the brain was assessed by quantitative polymerase chain reaction (qPCR) and flow cytometry, respectively.

TREM1 transcription was induced after cerebral ischaemia-reperfusion, peaking at 1d and declining at 5-14 d after transient MCAO. On the contrary, mRNA levels of TREM2 declined at 1d after stroke, but increased at 2-7 d following transient MCAO. A contrasting profile of myeloid cell subpopulations contributed to the expression of TREM1 and TREM2 in the brain after stroke, suggesting a differential involvement of resident and blood-derived myeloid cell subsets.

Our results demonstrate that the expression of TREM1 and TREM2 receptors in the brain is modified by experimental stroke in a reciprocal manner. The contrasting profile of amplifying and inhibitory TREM expression over time suggests the involvement of different TREM receptors in distinct phases of the brain response to ischaemia. Therapeutic strategies aiming to modulate the TREM system might influence the neuroinflammatory balance after stroke towards resolution.

This study was supported by the Medical Research Council and the Biotechnology and Biological Sciences Research Council.

Poster Ref: P1-F-055

Theme: F: Nervous System Disorders

The 'legal high' dissociatives, diphenidine and methoxphenidine, have different effects on the rodent dopamine system.

Neela Dutta[1], Jolanta Opacka-Juffry[2], Alex Gant[3], Lisa Lione[3] and Colin Davidson[1]

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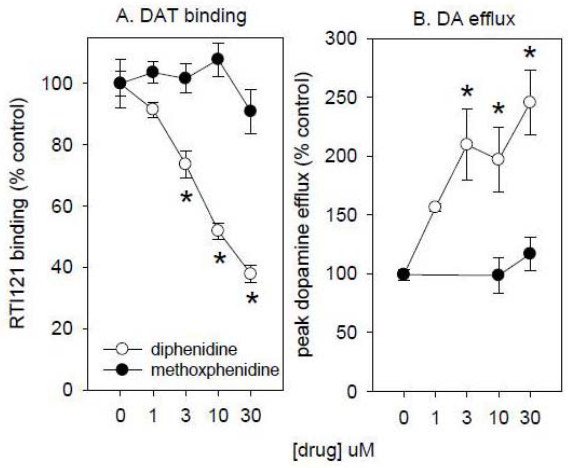
Introduction: Over the last 5-10 years there has been a huge increase in the number of new drugs of abuse, so called legal highs. These are drugs, which might resemble traditional drugs of abuse, but with their different chemical structure, are legal. Now referred to as 'new psychoactive substances' (NPS), one NPS that became popular around 2011 was a ketamine-like drug methoxetamine. It was branded as a bladder friendly ketamine, but was banned in the UK in 2013. However, 2 new dissociative NPS are currently being sold online: diphenidine and methoxphenidine. While these drugs are known to bind to the NMDA receptor, their effects at the dopamine transporter and bladder are unknown.

Methods: 8-week old male Wistar rats were used. Ligand Binding: 20 µm coronal sections of the nucleus accumbens were incubated with 20 pM [125I]RTI121 with increasing concentrations of diphenidine or methoxphenidine for 60 min (22°C) Slides were opposed to films for 3 days. Fast Cyclic Voltammetry: Accumbens brain slices were cut (0.4 mm). A triangular voltage waveform (-1 to +1.4 to -1V, 450 V/s) was applied to a carbon fibre electrode (CFE: 8 x 50 µm carbon tip), at around 0.6V a Faradaic current can be recorded from the oxidation of dopamine. The accumbens core was stimulated (10 pulses at 100 Hz) every 5 min. Drugs were added for 60 min.

Results: Diphenidine displaced RTI121 binding in a concentration-dependent manner ($F(4, 29) = 33.26$, $P < 0.001$) with 3, 10 and 30 µM causing a significant reduction in RTI121 binding ($p < 0.05$). There was no effect of methoxphenidine on RTI121 binding. Diphenidine increased peak dopamine efflux after electrical stimulation ($F(4, 24) = 8.63$, $P < 0.001$, with 3, 10 and 30 µM causing significant increases. Methoxphenidine had no significant effect on peak dopamine efflux. Effects on rat bladder contractions will be presented.

Conclusions: Diphenidine increased dopamine efflux, probably by dopamine transporter inhibition, whereas methoxphenidine had no significant effect on either RTI121 binding or evoked dopamine efflux. These data suggest that diphenidine might have some addictive liability, whereas methoxphenidine may not.



Poster Ref: P1-F-056

Theme: F: Nervous System Disorders

Developing a novel *in vitro* model of mitochondrial epilepsy: 'a dual neuronal – astrocytic hit hypothesis'.

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Up to a third of patients with mitochondrial disease develop epilepsy. Patients with mitochondrial epilepsy have extremely poor prognosis and a difficult to control epilepsy. Drug development in this field has been lagging due to a lack of good functional models. Post-mortem neuropathology of temporal neocortex from patients with mitochondrial epilepsy has shown deficiency in mitochondrial respiratory chain complexes I and IV in both GABAergic interneurons and astrocytes, with a pattern of astrogliosis. Building on these observations, we aim to develop a novel *in vitro* brain slice model of mitochondrial epilepsy using various mitochondrial inhibitors; rotenone (complex-I inhibitor), potassium cyanide-KCN (complex-IV inhibitor), and fluorocitrate (astrocytic specific aconitase inhibitor.

Epileptic activity was readily generated in both the hippocampus (CA3) and temporal neocortex by adding fluorocitrate (0.1 mM) followed by co-application of rotenone (500nM) and KCN (10μM). Applying either fluorocitrate or rotenone-KCN alone did not generate any epileptic activity. We have also replicated these experiments in surgically resected human temporal neocortical slices from patients undergoing amygdalohippocampectomy or tumour removal (n=6). Six commonly used conventional antiepileptic drugs – carbamazepine, lamotrigine, levetiracetam, sodium valproate, midazolam, and sodium pentobarbital - were tested and all the drugs but sodium pentobarbital failed to suppress the epileptic activity. Post-hoc immunohistochemistry of these epileptic brain slices showed a pattern of astrogliosis. There was also a significant reduction in the population of GABA-ergic interneurons (n=5), especially parvalbumin-expressing interneurons (n=6) and calbindin-expressing interneurons (n=5), in the hippocampus CA3 while relatively sparing the excitatory pyramidal neurons (n=3).

In conclusion, we have successfully developed a novel *in vitro* brain slice model for mitochondrial epilepsy. It replicates most of the features seen in the human neuropathology and also shows pharmacoresistant properties. Together, the data suggest a susceptibility of inhibitory interneurons towards mitochondrial dysfunction, that when coupled with astrocytic impairment, could lead to epileptogenesis.

Poster Ref: P1-F-057

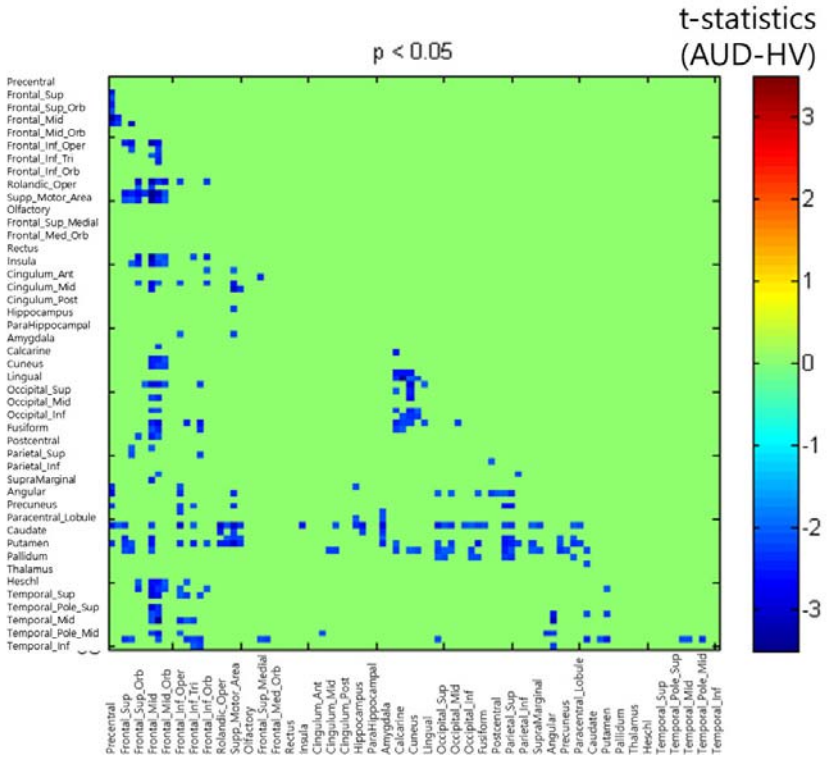
Theme: F: Nervous System Disorders

Disrupted modular structures in resting state brain network of patients with alcohol use disorder.

Kwangyeol Baek, Laurel Morris and Valerie Voon

University of Cambridge

Chronic alcohol consumption impairs brain functions and structures, inducing compensative changes over the global brain network. Alcohol use disorder (AUD) have been also associated with impulsivity/compulsivity traits and disruption on the cortico-striatal brain network. Here we aimed to examine global network structure in resting state brain of patients with alcohol use disorders. Using 3T Siemens MRI scanner, we took multi-echo resting state BOLD fMRI scans from 36 patients with AUD, 36 age-matched healthy controls and 32 younger subjects with binge drinking habits (BD). Non-BOLD noises in the resting stat fMRI data was removed using Multi-Echo Independent Component Analysis (ME-ICA) pipeline, and functional connectivity in 90 ROIs of the Anatomical Automatic Labeling template was estimated. Complex network properties such as local and global efficiency, assortativity and modularity were assessed after the functional connectivity matrices were binarized with density threshold of 5~30%. Modular structure of resting state functional connectivity were disrupted in AUD patients compared to healthy controls and BD subjects. AUD patients exhibited significantly decreased modularity and increased assortativity compared to healthy controls and BD subjects. In AUD patients, hub regions were more likely to be connected with other hub regions and functional modules were less segregated from each other. However, global or local efficiency of the network were not significantly affected in AUD patients. In AUD patients, region-to-region functional connectivity was decreased in the DLPFC (middle frontal gyrus), mOFC, caudate and putamen as shown in Fig. 1. These decreased connectivity weights did not affect network efficiency in global or local scale, but might be related with disrupted modular structures in the resting state brain network of AUD patients.



Group difference in region-to-region functional connectivity: Patients with alcohol use disorder vs. Healthy controls (t-statistics, only shown for $p < 0.05$).

Poster Ref: P1-F-058

Theme: F: Nervous System Disorders

Polysialylated neural cell adhesion molecule (PSA-NCAM): a therapeutic target for regenerative human monoclonal antibody HIgM12 for treatment of multiple sclerosis and neurodegenerative disorders.

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Introduction: Demyelinating and neurodegenerative diseases form a significant proportion of neurological disorders. Current therapeutic strategies of immunomodulation are not known to reverse disability or improve long-term prognosis. Approachable molecular targets stimulating CNS repair have not yet been identified. A natural human monoclonal autoantibody, HIgM12 capable of reversing motor deficits in a mouse model of MS has been identified. The aim of the project is to identify the antigen to HIgM12.

Methods: Total adult mouse brain lysate was prepared from CD1 and C57/Bl6 mice and analysed by immunoprecipitation and western blotting. The HIgM12 antigen was enriched and sent for mass spectrometry analysis. The antigen was identified using different NCAM knockout strains and through PSA removal. Its effects on antibody-binding, antibody-mediated cell adhesion and neurite outgrowth were assessed with western blotting, immunoprecipitation, immunocytochemistry and histochemistry.

Results: Western blotting showed binding of HIgM12 to multiple bands migrating between 140-200kDa. Immunoprecipitation and visualization of the protein produced bands of similar molecular weight. Mass spectrometry identified high percentage sequence coverage in the isolated protein band with neural cell adhesion molecule (NCAM). HIgM12 binding was absent in the CNS of NCAM knockout mice. Antibody-binding to cell surface antigens on oligodendrocyte progenitor cells and astrocytes from WT animals was present but not in NCAM knockouts *in vitro*. Immunocytochemistry showed 95-100% co-localisation between HIgM12 with NCAM in wild-type astrocytes. Using a PSA-NCAM antibody, we were able to identify identical staining patterns of astrocytes from WT and NCAM KO mice between PSA-NCAM and HIgM12. Western blotting also demonstrated identical molecular weight of bands detected between the PSA-NCAM and HIgM12 antibodies. Our study also showed the HIgM12 antibody was unable to identify its antigen in the absence of PSA, indicating PSA is required for HIgM12 binding to NCAM.

Conclusion: This study concludes that HIgM12 mediates its *in vivo* and *in vitro* effects through binding to PSA-NCAM and has the potential to be an effective therapy for MS and neurodegenerative diseases.

Theme G: Methods and Techniques

Posters P1-G-001 to P1-G-015

Poster Ref: P1-G-001

Theme: G: Methods and Techniques

Laminar specific neural activation *in vivo* with a high-density micro-LED array.

Tomomi Tsunematsu[1], Robert Scharf[2], Martin Dawson[2], Keith Mathieson[2] and Shuzo Sakata[1]

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Manipulation of neural activity is a powerful approach to uncover a causal link between neural activity and behaviour. Although optogenetics offers innovative ways to achieve this in a cell-type-specific manner with millisecond precision, most of current optogenetic approaches suffer from their limited spatial resolutions. For example, while the six-layered structure of the neocortex is one of the most prominent anatomical features in the mammalian brain, it is still challenging to activate different cortical layers in a single animal even with genetic manipulations and advanced optical approaches. Here we use a novel high-density micro-LED probe to overcome this. The probe contained 16 individually controllable micro-LEDs, each of which emits at a peak wavelength of 450 nm with irradiance levels controllable from 1 to 300 mW/mm2. We have validated this technology by showing laminar specific activation *in vivo* through two experimental approaches. In the first experiment, as a proof-of-concept study, we activated channelrhodopsin-2 (ChR2)-expressing parvalbumin positive (PV+) interneurons in a laminar specific manner by penetrating the neocortical laminae with both the micro-LED probe and a conventional optrode, which contained 32 channel recording sites with an optical fiber. Although the conventional, optical fiber based approach, activated PV+ neurons across cortical layers, local illuminations with micro-LEDs modulated PV+ neuronal activity only in specific layers. In the second experiment, we utilized Emx1-Cre mice to express ChR2 in the entire cortical layers and investigated how neural activation propagated in the cortical column. Whereas the conventional surface illumination generated strong activation in superficial layers as expected, the micro-LED stimulations could generate distinct spatiotemporal patterns of population activity across layers depending on illumination sites. Importantly, this was achievable in a single animal without other genetic manipulations. Thus, our micro-LED probe offers a new way to manipulate neural activity with high spatial resolution *in vivo*. We will further discuss potential applications of this technology for neural circuit analysis.

Poster Ref: P1-G-002

Theme: G: Methods and Techniques

The diagnostic and discriminative validity of three neuropsychological screening tests: MMSE, TYM and MoCA.

Clara Calia[1], Lucia Destino[2], Alessandro Semeraro[2], Michele Pennelli[2] and MariaFara DeCaro[2]

[1]Queen Margaret University, Edinburgh, [2]University of Bari, Italy

Background: The increasing prevalence of people with Alzheimer's disease (AD), as well as the high financial and emotional costs associated with this diagnosis; make early detection of an individuals risk for Alzheimer's disease a high priority.

Neuropsychological assessment is essential in determining the percentage of MCI (Mild Cognitive Impairment) conversion to dementia (Gagnon and Bellville, 2011).

Objective: This study investigated the diagnostic and discriminative validity of three neuropsychological screening tests: the Mini Mental Status Examination (MMSE; Folstain, 2000), the Montreal Cognitive Assessment (MoCA; Nasreddine *et al.*, 2005) and Test Your Memory (TYM; Brown, 2009)

Materials and Methods: The study included 120 people divided in 3 groups according to their diagnosis: MCI (median age: 70.46 years, SD = 8.1, range 54-84; median years education: 8.4, SD = 3.7), AD (median age: 73.92 years, SD = 8.9, range 50-90; median years education: 6.62, SD = 4.4) and subjective memory disorder (median age: 66.94 years, SD = 7.5, range 55-84; median years education: 11.46, SD = 5.3). Each participant was assessed with MMSE, TYM and MoCA.

Results and Conclusion: The overall scores from the battery of tests showed that each of these tests tend to under investigate specific cognitive functions: executive functions and visual-spatial skills in the case of MMSE, memory in the MoCA and attention in the TYM.

On the contrary, there are cognitive areas that have a specific relevance and which contribute significantly in the allocation of the overall score of the test: specifically orientation tasks are privileged in the MMSE and Moca, while language in the TYM.

The comparison between MMSE, MoCA and TYM shows that the cognitive variables have different weight depending on the test used.

In conclusion, the authors suggest the need for a unique test that combines the strengths of the three tests analysed in this study.

Poster Ref: P1-G-003

Theme: G: Methods and Techniques

A GCamp6 transient detection algorithm tto characterise neuronal population responses in layer 2/3 of mouse somatosensory cortex.

Caroline Copeland, Stephanie Reynolds, Luca Annecchino, Jon Oñativia, Pier Luigi Dragotti and Simon Schultz
Imperial College London

Understanding the functional principles of the mammalian cortical circuit is one of the major projects of modern neuroscience. To progress on this problem, we need to observe the behaviour of the individual neuronal elements of this circuit. Whole-cell patch-clamping is the current gold standard technique as it allows recording of sub- and supra-threshold signals. However, it has largely been limited to investigating a single neuron at a time *in vivo*, and it is somewhat challenging to infer the times of sequences of action potentials from neurophysiological data. Detecting action potentials using two-photon calcium transient imaging offers advantages over standardised electrophysiological approaches as it enables up to thousands of spatially and immunohistochemically defined neurons to be recorded from simultaneously. Recently, we introduced a novel approach to the problem by making use of finite rate of innovation (FRI) theory (Vetterli *et al.* 2002 IEEE Trans. Signal Process. 50 1417-28). This enabled us to retrieve the timing of action potentials from calcium transient time series using both surrogate data and real data (obtained by simultaneous electrophysiology and two-photon imaging of calcium dye signals in cerebellar Purkinje cell dendrites) (Oñativia *et al.* 2014 J. Neural Eng. 50 046017). We have now extended and optimised this algorithm to detect specific calcium transient kinetics reported by the genetically encoded calcium indicators GCaMP6s and GCaMP6f. We achieved this by first performing test simulations using surrogate data, before introducing real data from single-neuron and population responses to vibrissae deflection in layer 2/3 of identified columns in mouse somatosensory (barrel) cortex, using *in vivo* two-photon imaging. Implementation of this algorithm will prove a useful tool for analysis of neuronal network dynamics both within the somatosensory cortex, and across additional cortical areas associated with other sensory modalities (*e.g.* vision, audition, proprioception).

Poster Ref: P1-G-004

Theme: G: Methods and Techniques

Development of a robust and reproducible method of human neurite outgrowth and its application to study the mechanisms of neurite inhibition within the glial scar.

Kirsty Clarke[(1)], Andrew Whiting[(1)] and Stefan Przyborski[(1,2)]

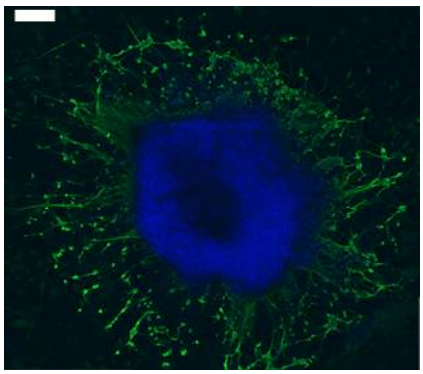
[1]Durham University, [2]Reinnervate Ltd, Sedgefield

Introduction: Injury to the spinal cord results in an inhibitory environment due to the activation of astrocytes and the release of molecules that supress neurite growth; this is known as the glial scar. Inhibitory molecules are released from damaged myelin and reactive astrocytes and act through receptors to inhibit neurite outgrowth. The detailed molecular mechanism of their action is relatively unknown. We have developed a novel *in vitro* human pluripotent stem cell based model of neuritogenesis, to support the investigation of the molecular mechanisms that underpin neurite inhibition.

Methods: Human pluripotent stem cells were cultured in suspension at a density of 1.5x106 cells per Petri dish 24 hours prior to retinoid treatment. Stem cell aggregates were maintained with retinoids for 21 days before being transferred to either a 48-well tissue culture plate or a 3D polystyrene scaffold coated with poly-D-lysine/laminin. Aggregates were fixed with 4% PFA following 10 days culture with mitotic inhibitors and prepared for immunocytochemistry prior to quantification.

Results: Human stem cell aggregates differentiated with both the naturally occurring all-trans retinoic acid (ATRA) and more photostable synthetic retinoids (EC23, AH61) formed multiple TUJ-1 positive neurites that radiate from the central aggregate. Synthetic retinoids induced neurite outgrowth to a greater extent than ATRA. Treatment with 0.01μM EC23 produced significantly more neurites than any other condition tested with an average length of 400μm, and the advantage of increased compound stability. Additionally, when cell aggregates were cultured on a porous, polystyrene scaffold, 3D neurite outgrowth can be observed throughout the scaffold.

Discussion: The data demonstrate that synthetic retinoids can efficiently induce neural differentiation of human pluripotent stem cells, resulting in significant neurite outgrowth in a robust and reproducible manner. The optimum condition to promote neurite outgrowth from stem cell aggregates was found to be 0.01μM EC23. This model is now being adapted into a 3D culture environment to provide a more physiological system to apply neurite outgrowth inhibitory molecules and investigate the molecular mechanisms that govern neurite inhibition.



Expression of the pan neuronal marker TUJ-1 from a representative human pluripotent stem cell aggregate differentiated with 0.01μM EC23. TUJ-1 positive neurites radiate from the central aggregate. DAPI highlighted nuclei are stained blue. Scale bar: 200μm.

Poster Ref: P1-G-005

Theme: G: Methods and Techniques

MATLAB scripts for characterising multiple single-unit spike trains: a study of rat medial prefrontal cortex & hippocampus.

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Interpretation of multi-electrode electrophysiological data sets require time efficient processing and data visualisation during screening of spike train activity, correlated neural activity between units and characterising Up-Down states. We illustrate the application of scripts to neural ensemble interaction within the medial prefrontal cortical (mPFC) sub-regions and between the mPFC and hippocampus in the rat.

Lister-hooded rats were anaesthetised with isoflurane (50%N_2O:50%O_2), with microelectrode arrays to record from the mPFC (cingulate gyrus & prelimbic areas) and hippocampal single-units and local field potentials (LFPs) using a Plexon MAP system. All experiments were performed in accordance with the Animals (Scientific Procedures) Act 1986 UK. Sorted spike train and LFP data were initially analysed with NeuroExplorer, then exported and processed using custom-written Matlab scripts (www.nottingham.ac.uk/neuronal-networks).

SpikeTrainClusterAnalyser script: Firing rate statistics were calculated with firing rate histograms with 1-min bins normalized to a user-defined mean baseline firing of individual units. Z-score normalization was used to allow comparison across the unit populations (either single or group experiments) with various firing rates. K-means cluster and hierarchical cluster analysis were used to detect any predominant patterns of responses to treatment or stimulus events. To aid user identification, computed clusters were visualised with silhouette verification & 3-D principal component analysis and the sorted multiple unit recordings displayed as colour-coded spike rastergrams, with the z-axis colour proportional to the firing rate. The plots allow users to compare and visualise any spike train neural activity changes induced by behavioural or drug-induced events.

XcorrelationGrid script: Provides a graphical visualisation and evaluation of cross-correlation histograms (CCHs) of multiple unit-pairs from a recorded population, the resultant grid displaying reference (y-axis) vs. target (x-axis) units and the z-axis colour proportional to the degree of correlation.

SynchronyIndex script: computes and plots synchrony of firing patterns within user-assigned population(s) of recorded single-units computed over successive defined epochs.

Poster Ref: P1-G-006

Theme: G: Methods and Techniques

Transcranial direct current stimulation (tDCS) and cognitive training in traumatic brain injured patients: focus on divided attention and its neural and behavioural correlates.

Valentina Galetto[1,2], Danilo Dimitri[2], Elisabetta Geda[1,3], Francesca Perotti[4], Davide Vilella[4], Marina Zettin[1,2], Giuliano Geminiani[1] and Katiuscia Sacco[1,3]

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Divided attention is defined as the ability to distribute cognitive resources among two or more simultaneous tasks. Following severe traumatic brain injury (TBI) such a function could be compromised, resulting in problems in numerous activities of daily living. So far, there have been few studies aimed at analyzing the effect of cognitive rehabilitation on divided attention improvement. Main purpose of this research is to assess the efficacy of combined tDCS and computer based training on the improvement of divided attention in brain injured subjects. Specifically, we focused on the behavioural and neural modifications induced by such a treatment.

Sixteen subjects with a severe traumatic brain injury participated in the study. They were submitted to a neuropsychological evaluation one month prior to the beginning of the experiment (T0). This evaluation was repeated the day before the training (T1). In this occasion, each subject was also submitted to an fMRI session. The training was characterised by 20'of tDCS, administered twice a day for 5 days. The electrodes were placed on the dorso-lateral prefrontal cortex, but their specific placement varied for each patient, depending on the location of the injury. After each session, the patient received 40' of a computerized cognitive training. At the end of the treatment (T2) TBI subjects were submitted to a third neuropsychological assessment, followed by a second fMRI session. Furthermore, two follow-up sessions were performed (1 and 6 months after the end of the training) to verify maintenance of results.

Outcomes of the study highlighted an improvement of divided attention only between T1 and T2, resulting in faster reaction times (p=.0001), associated with decreased omissions (p= .0001). Such an improvement was kept in both the follow up sessions. Neuroimaging data resulted in a cerebral reorganization, associated with a lower but more functional neural activation following the training. It follows that the cognitive changes observed after our treatment may be related to modulations of neural plasticity. This neural reorganization may be explained as a sort of "balance mechanism": neural activations, which were wider and more generalized before the training, became more focal and task-specific after it.

Poster Ref: P1-G-007

Theme: G: Methods and Techniques

Characterisation of temporal nitric oxide release profiles from nitric oxide donors.

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MRC Toxicology Unit, Leicester

Nitric oxide (NO) is a highly reactive and freely diffusible molecule that plays major roles in a myriad of physiological processes ranging from regulation of blood pressure to synaptic plasticity. NO elicits these effects through different pathways, which are largely dependent on the concentration of NO produced. At low concentrations, NO generation from nitric oxide synthase (predominantly neuronal or endothelial nitric oxide synthase) leads to activation of soluble guanylyl cyclase and generation of cyclic guanosine monophosphate which activates a wide range of signalling molecules such as protein kinases. At higher concentrations, NO release leads to post-translational modifications such as S-nitrosylation of cysteine residues and tyrosine nitration, both of which alter protein function, usually detrimentally. The study of NO signalling usually involves application of exogenous NO *via* various donors. However the main caveat using NO donors is the unknown release capacity of each donor. This has led to countless publications of contradictory findings due to the use of different donors and concentrations across studies. In order to better characterise the release profile of NO from commonly used NO donors, we measured temporal release profiles following varying storage times at 4°C and -20°C of different donors at multiple concentrations. NO release was detected in standard phosphate buffered saline over time using NO sensing electrodes. The NO microsensor chosen for this study (NOPF100; World Precision Instruments Ltd) possess a multi-layered selective coating that eradicates non-specific detection providing reliable NO measurements. We found that donors such as NOC-5 and PAPA NONOate initially release high levels of NO but decay substantially within days, whereas SNP and GSNO stocks show greater stability in solution releasing consistent and lower levels of NO over several days. Furthermore, in all donors tested, the amount of released NO differs between long-term frozen and fresh stock solutions. Therefore our data provides a systematic and comprehensive comparison of NO release by different donors which provides crucial information for studying nitrergic signalling and allows a better evaluation of reported nitrergic signalling outcomes.

Poster Ref: P1-G-008

Theme: G: Methods and Techniques

Micro-LED probes for site-specific optogenetic activation of neural circuits at depth.

Robert Scharf[1], Tomomi Tsunematsu[2], Dandan Zhu[3], Erdan Gu[1], Ian Watson[1], David Wallis[3], Colin Humphreys[4], Martin Dawson[1], Shuzo Sakata[2] and Keith Mathieson[1]

[1]Institute of Photonics, University of Strathclyde, [2]Strathclyde Institute of Pharmacy and Biomedical Sciences, [3]Plessey Semiconductors Ltd, Plymouth, [4]Department of Materials Science and Metallurgy, University of Cambridge,

Optogenetics has become a popular technique for studying neural circuits in recent years, when many different opsins have been developed, tuned to different wavelengths and showing different sensitivities and kinetics. However, the technology for delivering light to sub-populations of neurons in deeper brain structures is still lagging behind, with the conventional focus being on multi-photon techniques and fibre-optics.

Here we show a new device for light delivery at depth using micro-LEDs. We have developed and fabricated a needle-shaped probe for direct brain penetration, which consists of sixteen 25 μm-diameter LEDs linearly-spaced over 750 μm. This allows precise spatiotemporal patterns of activation and therefore a more detailed study of neural circuits, such as the laminar structure of the neocortex. The work was performed with high-performance GaN LED epistructures grown on 150-mm silicon substrates and emitting at ~450 nm, to which standard microfabrication techniques were applied. Monte Carlo simulations indicated that channelrhodopsin2 (ChR2) activation is possible up to ~250 μm from the LED surface. Silicon's good mechanical and thermal properties made a compact design possible (100 μm × 30 μm × 3 mm), minimising tissue damage during probe insertion.

In-vivo experiments were conducted in mice expressing ChR2 in the neocortex, where our LED probe was paired with a 32 channel linear recording electrode probe. Electrodes that were ~80-100 μm from the LED probe recorded action potential firing rates of ~100 Hz at 120 mW/mm2 LED irradiance, with layer specific accuracy possible by activating neighbouring μLEDs. Next steps include scaling up the number of LEDs and using other wavelengths, for the control of different types of opsins. Our device is compact and can therefore be easily used in any lab to address various questions in systems neuroscience.

Poster Ref: P1-G-009

Theme: G: Methods and Techniques

Towards a gold-standard for combined TMS and EEG data pre-processing: a critical examination of the effectiveness and reliability of a two tiered independent components analysis approach.

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Background: Combining transcranial magnetic stimulation (TMS) & electroencephalography (EEG) has the potential to expand our understanding of cognitive processes, yet its progress is slowed by the effects of stimulation induced artefacts on the data. Of the methods for TMS artefact removal, independent components analysis (ICA) has seen the most advances. However, the lack of a standard protocol for ICA based TMS artefact removal hinders comparisons between studies. The aims of this study were to evaluate the efficacy of a standardised protocol for TMS artefact removal using ICA, and to determine its reliability.

Methods: Six participants received occipital TMS, using a figure of eight coil, whilst undergoing 128 channel EEG recorded on a standard amplifier. Two sequential rounds of ICA were applied. The first focussed on identification and removal of artefactual components explaining the greatest proportion of the variance between -40 and +40ms. These served as sources of the decay/recovery artefact, and early muscular responses to TMS. The second round of ICA was performed to identify and remove sources of smaller artefacts present up to 500ms post stimulation.

To assess the effect of component removal on signal quality the amplitude of the global field power (GFP) 20ms post stimulus, and the number of GFP maxima associated with the TMS evoked potential (TEP) were recorded at each stage of the protocol. To test the efficacy and reliability of the method the protocol was performed three times per participant. The amplitudes and number of peaks were compared before cleaning and after each round of ICA, within and between cleanings using Friedman's analysis of variance.

Results: Component removal reduced the amplitude of the signal within the pulse recovery period whilst maintaining the TEP structure. This effect was observed on all occasions for each participant, and achieved without significant differences in the number of components removed.

Conclusions: We present evidence for the effective and reliable removal of TMS artefacts from EEG data using a standardised ICA based protocol. We demonstrated that using this procedure yields a clean and unbiased TEP waveform, as indexed by the GFP, thus providing a viable methodology for dealing with artefacts in TMS-EEG.

Poster Ref: P1-G-010

Theme: G: Methods and Techniques

Optogenetic tools to study subpopulations of dopamine neuron with different vulnerability to Parkinson's.

Neil Blackledge[1], Javier Alegre-Abarrategui[2], Stephanie Cragg[2], Richard Wade-Martins[2] and Sarah Threlfell[2]

[1]Dept. Biochemistry, University of Oxford, [2]Dept. Physiology, Anatomy and Genetics, University of Oxford

Following the emergence of optogenetics in neuroscience to study specific neuronal populations we aimed to develop this technology in a dual-recombinase approach to study subpopulations of dopamine (DA) neuron which are differently vulnerable to Parkinson's.

Subpopulations of DA neuron are differently vulnerable to degeneration in Parkinson's. DA neurons which contain the calcium binding protein calbindin (Calb1) are less vulnerable to Parkinson's. An understanding of the different mechanisms operating within and the functions of subtypes of DA neuron may hold the key to understanding cell-specific neurodegeneration in Parkinson's disease. We have created FRT- and loxP-flanked viral constructs and a Calb1 Flpo-recombinase transgenic mouse for use in a dual-recombinase strategy to target expression of channelrhodopsin (ChR2) to defined subtypes of DA neuron.

Two viral constructs were made by modifying a Cre-dependent ChR2 expression construct by flanking the ubiquitous EF-1a promoter with 2 pairs of FRT sites. A bacterial artificial chromosome (BAC) containing the mouse Calb1 locus was modified using Red/ET recombination to incorporate Flpo-recombinase at the first exon of Calb1. This BAC was used to create a Calbindin-Flpo transgenic mouse by pronuclear microinjection.

The two modified viral constructs are able to direct expression of ChR2 *in vitro* to cells expressing either Cre-recombinase alone or both Cre- and Flpo-recombinase. Founder lines of the Calb1-Flpo mice have been created; initial characterisation of these lines will be presented.

Generation of these tools will allow us and others to reveal key characteristics of vulnerable versus resilient DA neurons that could offer insight into our understanding of Parkinson's disease.

Poster Ref: P1-G-011

Theme: G: Methods and Techniques

Retinal biomarkers for Alzheimer**'s disease in people with Down's syndrome.**

Madeleine Walpert[1], M. Francesca Cordeiro[2], Eduardo Normando[2], Shahid Zaman[1] and Anthony Holland[1]

[1]Cambridge Intellectual and Developmental Research Group, University of Cambridge, [2]Institute of Ophthalmology, University College London

Our aim is to examine the potential for retinal changes as an early biomarker for Alzheimer's disease (AD) in people with Down's syndrome (DS), who are known to have high prevalence and early onset of AD. This study will assess the acceptability and feasibility of spectral-domain optical coherence tomography (SD-OCT), which has not previously been used in the DS population, to detect retinal nerve fibre layer defects in people with DS, and will compare the results to those found in AD of the general population. We will also incorporate a new technique, Detection of Apoptosing Retinal Cells (DARC), which has the capability of visualising individual cell death *in vivo* and will be done so in a population at high risk of AD for the first time.

This cross-sectional study will include 30 participants with DS (aged 18+) and 30 healthy age and sex-matched controls. High-resolution OCT examinations of the peripapillary and macular retinal nerve fibre layer (RNFL) thickness will be obtained and apoptosis will be measured using a confocal scanning laser ophthalmoscope (cSLO). Participants with DS will also have MRI (magnetic resonance imaging) and PET (positron emission tomography) brain scans and degeneration seen in the eyes will be correlated to amyloid-beta (Aβ) build-up and atrophy in the brain. Cognitive function and diagnosis of dementia will be assessed.

We anticipate that the RNFL will be significantly thinner in participants with DS than healthy controls and that this will be increased in those with clinical dementia and will correlate with the Aβ and atrophy seen in the brain scans. Likewise we expect to see an elevated quantity of apoptosing retinal ganglion cells which will correlate with brain atrophy. We also hypothesise that reported behavioural and personality changes will predict impairment in measure of executive functioning and working memory and will be associated with retinal degeneration.

Retinal biomarkers have the potential to provide an insight into the natural progression of AD. Early markers of AD-related change are necessary to aid the development of treatments and therapies. It is understood that an increase in knowledge of AD in DS will benefit AD in the general population due to the similarities in the manifestation of the disease.

Poster Ref: P1-G-012

Theme: G: Methods and Techniques

A microfluidic perfusion system for studying functional connectivity between *in vitro* neuronal co-cultures.

Graham Robertson, Michele Zagnoni and Trevor Bushell

University of Strathclyde

In vitro mixed neuronal/glial cell cultures are a valuable tool for studying fundamental cellular mechanisms and the changes that occur during neurodegenerative conditions. Recently, microfluidic techniques have become a popular method to enhance standard *in vitro* procedures where cells can be patterned and the fluidic environment of the cultures can be precisely controlled. One of the platforms that are used involves two individual culture chambers that are separated by an array of microchannels which allows neurites to grow across forming synapses with the twin culture. This allows one network to be chemically stimulated while both presynaptic and postsynaptic responses can be observed simultaneously. However, current methods of washing drugs on and off of a neuronal network in such a device are often performed manually or are incapable of switching between multiple perfusates which limits the usefulness and repeatability of such systems.

We have developed a microfluidic perfusion system that can reliably switch between multiple perfusates. This was applied to a single compartment of interconnected, yet environmentally isolated, primary hippocampal co-cultures where the cellular activity was monitored using calcium imaging. The system did not affect the viability of the cells as cultures (10-14 DIV), which were repeatedly exposed to glutamate (100 μM) for 30-40 seconds, remained functionally active over the course of 1 hour. To demonstrate the capability of delivering multiple drugs in sequence using the system, responses to glutamate (10 μM) were abolished with the use of perfusates containing the glutamate antagonists, NBQX (20 μM), DL-AP5 (100 μM), and MCPG (500 μM).

The perfusion system developed exploits automated equipment making it possible for the process to be scaled into a high throughput platform. Overall this system can be used to study neurological mechanisms in a controlled manner and has the potential to be used in the screening of novel drugs and therapeutics targeted at neurodegenerative disorders.

Poster Ref: P1-G-013

Theme: G: Methods and Techniques

PET imaging of neuroinflammation in a rat contusion spinal cord injury model using the TSPO ligand 18F-GE-180.

Jordi L.Tremoleda[1], Meirion Davies[1], Julie Foster[2], Imtiaz Khan[3], Orli Thau-Zuchman[1], Jane Sosaboswki[2], William Trigg[3] and Adina Michael-Titus[1]

[1]Centre for Trauma Sciences. Barts QMUL, [2]Barts Cancer Institute. QMUL, [3]GE Healthcare Ltd

Traumatic spinal cord injury (SCI) is a devastating insult affecting ~2.5million people worldwide. It leads to substantial disability and is associated with a high socio-economic burden. There are currently no effective treatments. The modulation of the growth-inhibiting environment driven by the neuroinflammatory response after injury has evolved as a major therapeutic strategy. Thus, *in vivo* monitoring of the microglial response after SCI is key for diagnostics. Upregulation of the translocator protein 18 kDa(TSPO) is a hallmark of activated microglia and can be used for neuroimaging . The aim of this study is to assess the application of a clinically relevant molecular target for NI in a contusion SCI rat model using a novel PET ligand with high affinity and selectivity for TSPO. Adult male Wistar rats (n=22) were subjected to laminectomy and subsequent controlled contusion at the T10 spinal cord segment. Non-injured (n=6) and T10 laminectomy only (Lam; n=10) animals were used as controls. A subset of SCI animals (n=8) were treated with a single dose (i.v.) of a neuroprotective agent (docosahexaenoic acid,DHA) 30 min post-injury; a saline-injected group was used as control (n=6). PET/CT imaging was carried out at day 7 post-injury using the 18F -GE-180 radiotracer. After imaging, the spinal cord was harvested for biodistribution and autoradiography studies. *In vivo* dynamic PET imaging revealed an increase in the tracer uptake in the T10 injured spine compared to non-injured and Lam animals from 40 min post-injection ($P<0.0001$, 2way-ANOVA; SCI vs. Lam vs. non-injured). Biodistribution and autoradiography studies confirmed the high affinity and specific 18F-GE-180 binding in the injured spinal cord compared to the control groups. Interestingly, dynamic PET studies and biodistribution assays also showed a differential tracer uptake in the injured T10 spinal cord area in the SCI-DHA group compared to the saline group ($P<0.001$; ANOVA), supporting the NI modulatory role of DHA. These studies show that 18F-GE-180 PET imaging reveals differential radioactivity uptake that can be detected and visualised *in vivo*, offering a minimally invasive approach for monitoring neuroinflammation in SCI models and provide a meaningful clinical readout for testing new therapies.

Poster Ref: P1-G-014

Theme: G: Methods and Techniques

Analysis of resting state fMRI connectivity by local bold signal synchrony.

Gregory Kirk[1], Thomas Blumensath[2], Rasmus Birn[3] and Andrew Alexander[4]

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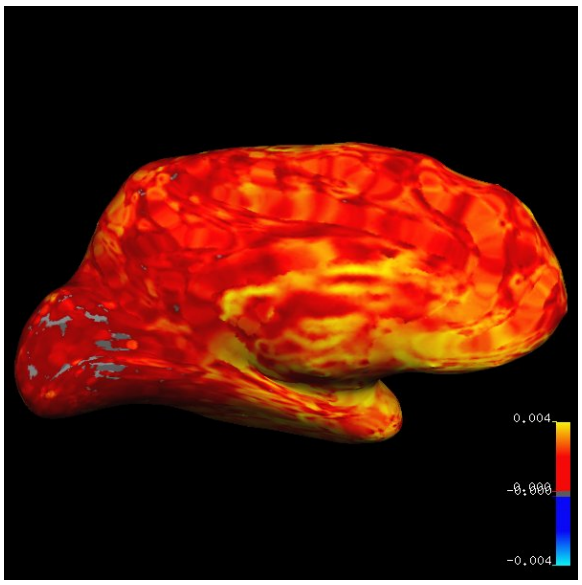
We present a metric that indicates all points on the cortical surface that are engaged in large scale connectivity at scan time. The metric is a measure of fMRI signal synchrony within a small neighborhood of a point. Functional connectivity analyses have been dominated by two types of procedures. Seed based methods indicate only the connectivity related to a chosen seed point. Independent component analysis assume that connectivity across the cortical surface may be represented by a small number of nodes. Evidence is provided that indicate both of these analyses provide either partial or only statistical average characterization of the functional connectivity of the cortex.

We demonstrate a relationship between the degree of synchrony of a neighborhood of a point and the global scale of functional connectivity of the point. We establish the generality of the relationship using a test retest data set. The data consists of six 10 minute resting fMRI scans obtained during the same scan session from each of 20 subjects. We derive the relationship by computing the seed based connectivity map for every point on the cortical surface.

With the results of the computation we have the relationship between the synchrony measure and the connectivity at each point of the cortical surface. The principal result is that large scale connectivity occurs only at points with highly synchronous neighborhoods. With this result generalized we show that we can visualize all points on the cortex that are engaged in large scale connectivity at scan time using the synchrony measure. The results provide evidence that previous characterizations of the cortex as being composed of a relatively small number of nodes may not be valid.

The data indicates a subset of the cortex in one of a small set of networks, while the majority of the cortex is composed of thousands of small functionally isolated islands. The set of points which are engaged in networks changes drastically between different scans within the same scan session with only the visual, motor and default mode networks remaining connected across all scans. We demonstrate a sliding time window analysis that indicates that even within a single scan the connectivity pattern changes dramatically over the course of the scan.



Left medial inflated cortical surface of a subject with synchrony measure overlay. High synchrony dark and low synchrony bright.dark areas have high connectivity over the entire time of the scan. Intermediate color only during part of scan duration.

Poster Ref: P1-G-015

Theme: G: Methods and Techniques

Novel objective physiological technique to quantify right hemisphere dominance.

Sanjeev Ramachandran, Usman Goga, Qadeer Arshad, Paresh Malhotra and Adolfo Bronstein

Imperial College London

Background: Right hemisphere dominance for visuo-spatial attention has been linked to anatomically larger fronto-parietal networks (Thiebaut de Schotten *et al.* 2011) and asymmetric parietal interhemispheric connections (Koch *et al.* 2011). We have previously shown that suppression of the left parietal lobe with trans-cranial direct current stimulation (tDCS) results in bilateral albeit asymmetrical suppression of the vestibular ocular reflex, elicited *via* caloric stimulation (Arshad *et al.* 2014). We propose that the inter-subject variability regarding the degree of nystagmus suppression is linked to individual differences in asymmetrical parietal interhemispheric connections.

Methods: 15 neurologically normal subjects (age 19-24; 7M) performed 10 bisection line trials, from which the mean deviation (mm) from the true centre was calculated. All subjects had a caloric before and after 15 minutes of left cathodal tDCS over the parietal cortex. The peak slow phase eye velocity (SPV) of the vestibular nystagmus was recorded before and after stimulation. Eye movements were recorded using infra-red video-oculography and SPV were plotted using an automated analysis programme (CHART VNG).

Results: Mean line bisection error and the degree of nystagmus suppression correlated negatively ($r^2=0.827$, $p<0.001$ Pearson correlation).

Conclusions: Our findings demonstrate that the degree of vestibular nystagmus suppression following tDCS application can be used as an objective physiological biomarker of parietal asymmetry. This index has the potential to be informative in the assessment of clinical syndromes associated with inter-parietal asymmetries.

Theme H: Autonomic Nervous System

Posters P1-H-001 to P1-H-006

Poster Ref: P1-H-001

Theme: H: Autonomic Nervous System

The effect of appetite on lateralized hypothalamic functional connectivity.

Hazel Wright[1], Xiaoyun Li[1], Nicholas Fallon[1], Timo Giesbrecht[2], Anna Thomas[2], Joanne Harrold[1], Jason Halford[1] and Andrej Stancak[1]

[1]University of Liverpool, [2]Unilever R&D

As the obesity epidemic continues, there is no definitive explanation for why some people become overweight while others do not. It is possible that differences in neural connectivity might be a risk factor for becoming overweight (Passamonti *et al.*, 2009).

Hypothalamus is the chief brain region for control of eating behaviour, and is anatomically and functionally connected with a number of homeostatic brain regions. To shed light on the role of hypothalamus during fasting and satiation, we took left and right hypothalamus as seeds and, using resting-state fMRI, mapped changes in functional connectivity induced by alterations in the homeostatic energy balance. Glycaemia, mood, hunger, and Three Factor Eating Questionnaire (Revised) data were also collected. Nineteen healthy people (9 male) participated.

During fasting we observed enhanced functional connectivity between left hypothalamus and inferior frontal gyrus, which was negatively correlated with body mass index. Following satiety, there was enhanced functional connectivity between right hypothalamus and superior parietal cortex. Both functional connections could be accounted for by differences in blood glucose levels, suggesting their association with metabolic energy balance. Both functional connectivities were significantly negatively correlated with cognitive restraint of eating; further, a significant proportion of the variance in BMI could be accounted for by the fasting functional connectivity between left hypothalamus and inferior frontal gyrus.

These areas appear to form a homeostatic energy balance network related to cognitive restraint of eating; preventing overeating when energy is depleted, and ending feeding or transferring attention away from food upon satiation. We suggest further research directions to explore the function of this homeostatic mechanism and its relationship to the risk of being overweight.

Poster Ref: P1-H-002

Theme: H: Autonomic Nervous System

Pro-opiomelanocortin neurones of the brainstem release opiates to suppress nociception, enhance vagal outflow and inhibit breathing.

Serena Cerritelli, Nina Balthasar and Anthony Pickering

University of Bristol

β-endorphin, an opioid linked with endogenous analgesia, is cleaved from pro-opiomelanocortin (POMC). One of the two central clusters of POMC containing neurones is in the nucleus of the solitary tract (NTS), which receives vagal afferent inputs. It is unclear if β-endorphin is released by NTS POMC neurones and what functional effect this might have. We hypothesised that activation of NTS POMC neurones would be antinociceptive and modulate vagal processing and respiratory activity within the brainstem *via* an opioid-mediated mechanism.

Viral vectors were used to exclusively target NTS POMC neurones in mice expressing Cre-recombinase in order to: (i) pharmacologically activate NTS POMC neurones, through expression of a designer 5-HT3 receptor (1), to examine influence on nociception using the tail-flick test; (ii) opto-activate NTS POMC neurones, through expression of Channelrhodopsin-2, to study effects on cardiorespiratory control in the working heart-brainstem preparation; and (iii) study the projections of NTS POMC neurones, *via* synaptophysin-mCherry expression to tag synaptic specialisations.

Pharmaco-activation of NTS POMC neurones, by administering a ligand to the designer receptor, significantly increased tail-flick latencies compared to saline at 30 and 45 min (n=8). This was abolished by naloxone (1mg/kg, IP; n=8). Opto-activation of NTS POMC neurones produced robust cardiorespiratory responses, including bradycardia, transient apnoea and increased respiratory sinus arrhythmia (n=20), which were attenuated by systemic naloxone (1μM; n=6). Synaptophysin-mCherry puncta were found at specific brainstem sites, including the NTS, periaqueductal gray, parabrachial nucleus, nucleus ambiguus and pre-Bötzinger complex (n=4).

These results show that activation of NTS POMC neurones can produce antinociceptive effects, exert a potent facilitatory influence on cardiac vagal outflow and can inhibit the respiratory network. These responses are likely to be mediated by β-endorphin. The tracing studies show that NTS POMC neurones are not simply local interneurones but form a class of projection neurones. NTS POMC neurones may have an opioid-mediated role in autonomic modulation and somatic nociception.

MRC and BPS funded.

1) Magnus CJ *et al.* (2011) Science 333, 1292-1296.

Poster Ref: P1-H-003

Theme: H: Autonomic Nervous System

Analytic tools for sympathetic nerve recordings in human.

Linford J.B. Briant, Laura E.K. Ratcliffe, Julian F.R. Paton and Emma C. Hart

BHI CardioNomics, University of Bristol

Microneurography is a powerful tool for directly recording muscle sympathetic nerve activity (mSNA) in humans with sympathetically-mediated diseases, such as essential hypertension and heart failure. Combined with continuous recordings of blood pressure (BP), ECG and respiratory parameters, a rich dataset is available that can be used to interrogate changes in the pattern of MSNA and any subsequent effect on cardiovascular function on a patient-by-patient basis. Given the recent advancements in treatments for drug-resistant hypertension (Esler, 2010; Paton, 2013), analytic tools that can quantify these physiological variables are essential, as the results may reflect mechanistic insight and inform novel treatment.

The difficulty analytically is the complexity of the dataset. Often mSNA is respiratory modulated, exhibits baroreflex-mediated inhibition, bursts in either clusters or singlets, and induces changes in vascular resistance of varying magnitude that last for 2-10 heart beats (Fairfax, 2013). Therefore, to understand how mSNA influences cardiovascular function requires efficient analytic techniques that can quantify mSNA and track cardiovascular parameters following bursts.

We present a set of analytic tools, constructed in the computing environment MATLAB, that are capable of characterising mSNA and its influence on cardiovascular parameters. This method can characterise baseline (~5min) recordings in <20s - quickly quantifying the properties of mSNA and the cardiovascular response. We have used these tools to analyse and compare datasets from a cohort of normotensive participants, and present the findings here. We suggest that these tools be combined into a MATLAB “toolbox” for analysing autonomic function in humans that is freely available to the wider scientific community, and welcome input into its content.

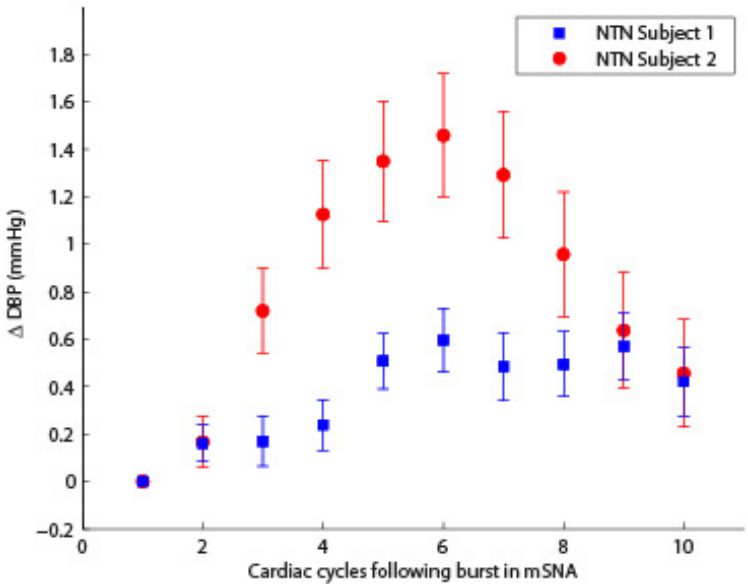
References:

S.T. Fairfax *et al.* J Physiol (2013).

M.D. Esler *et al.* Hypertension (2010).

J.F.R. Paton *et al.* Curr Hypertens Rep. (2013).

MATLAB, The MathWorks, Inc., Natick, Massachusetts, US.



Diastolic BP (DBP) response in 2 normotensive (NTN) subjects to mSNA bursts for 10 cardiac cycles following every burst. Subject 1 exhibits small DBP responses to mSNA bursts, whereas subject 2 exhibits large responses.

Poster Ref: P1-H-004

Theme: H: Autonomic Nervous System

Effect of deep brain stimulation on baroreflex modulation of sympathetic outflow in humans.

Yrsa Bergmann Sverrisdottir, Alexander L. Green, Tipu Z. Aziz, Nor Faizal Bahuri, Jonathan Hyam, Shanika D. Basnayake and David J. Paterson

University of Oxford

Electric deep brain stimulation (DBS) in midbrain nuclei in humans alters cardiovascular parameters, presumably by modulating autonomic and baroreflex function. Baroreflex modulation of sympathetic outflow is crucial for cardiovascular regulation and is hypothesized to occur at two distinct brain locations. This study aimed to evaluate sympathetic outflow in humans with DBS electrodes during ON and OFF stimulation of specific midbrain nuclei known to regulate cardiovascular function.

Muscle sympathetic nerve activity (MSNA) was recorded during DBS ON and OFF in patients with chronic neuropathic pain (n=7) and Parkinson's disease (n=10). Arterial blood pressure (ABP), heart rate and respiration were monitored during the recording session and spontaneous vasomotor and cardiac baroreflex sensitivity (BRS) were assessed. Head-up tilt testing was performed separately in the Parkinson's patients post-operatively.

Stimulation of the dorsal most part of the subthalamic nucleus (STN) and ventrolateral periaqueductal gray (PAG) resulted in improved vasomotor BRS, decreased MSNA burst frequency and arterial blood pressure (ABP), unchanged burst amplitude distribution and a reduced fall in ABP after tilt. Stimulation of the dorsolateral PAG resulted in a shift in burst amplitude distribution towards larger amplitudes, decreased spontaneous BP variability and unchanged burst frequency, BRS and ABP.

Baroreflex regulation of sympathetic outflow occurs in the STN and PAG. Our results may have implications in understanding abnormal sympathetic discharge in cardiovascular disease and provide an opportunity for therapeutic targeting.

Poster Ref: P1-H-005

Theme: H: Autonomic Nervous System

Activity in the micturition circuitry in the periaqueductal grey matter during voiding in anaesthetised rats.

Jonathan Crook and Thelma Lovick

University of Bristol

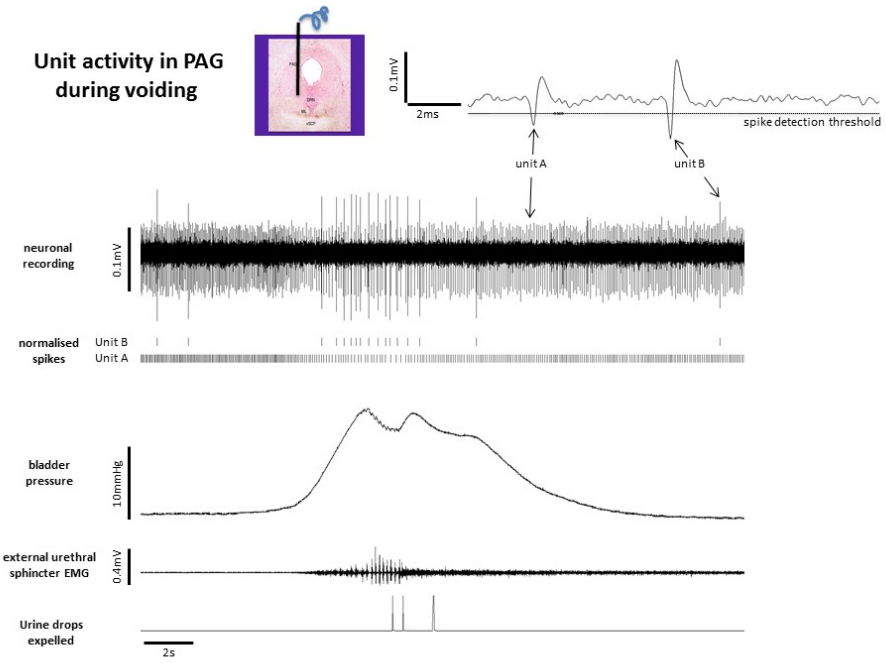
The functional integrity of a spino-midbrain-spinal loop relaying in the caudal ventrolateral periaqueductal grey matter (cvlatPAG) and pontine micturition centre (PMC) is a prerequisite for successful micturition. In order to understand more fully the role of the cvlatPAG in the control of micturition we recorded activity of neurons in this region during voiding. In urethane-anaesthetised rats (1.4g Kg-1 i.p.) repeated cycles of filling and voiding (0.1-1 min-1) were evoked by infusion of saline into the bladder (6ml h-1). During filling, bladder pressure rose gradually. Voids were characterised by a sharp rise in bladder pressure (up to 35 mm Hg), the development of bursting activity in the external urethral sphincter muscle (EUS) and expulsion of several drops of urine from the penis. The void terminated when EUS bursting activity ceased and bladder pressure returned to baseline.

The activity of 21/73 neurons recorded in the PAG and sub-adjacent region was time-locked to different components of voids. Of these, 6 (28.5%) increased their activity at the onset of the steep rise in bladder pressure signaling the onset of a void; firing of these cells returned abruptly to the pre-voiding rate as bursting activity developed in the EUS. The firing of 19% (n=4) also increased during bladder contraction but returned gradually to baseline as the bladder relaxed. One cell (5%) showed an increase in firing rate only during the period of bursting in the EUS.

10 cells were inhibited during voiding. In 6 of these (28.5% of the total responsive population) firing rate began to slow down as bladder pressure rose steeply and returned gradually to baseline as the bladder relaxed. One cell (5%) was inhibited during bladder contraction but showed an abrupt return to baseline when bursting activity in the EUS ceased. The remaining 3 cells (14%) decreased firing during bursting activity in the EUS.

We suggest that the PAG monitors bladder status and triggers the initial phase of voiding (bladder contraction). These events are ‘permitted’ by a lifting of the tonic inhibitory influence on the circuitry, which is present in between voids. Synchronisation of bladder and sphincter activity may occur further downstream, perhaps in the PMC.

Supported by the MRC project grant G1002251



Example of the activity of two neurons recorded simultaneously from a single electrode in the ventrolateral PAG during a void. Unit A is inhibited during the rise in bladder pressure, whereas unit B increased firing during bladder contraction but firing stopped abruptly when bursting activity in the external urethral sphincter EMG ceased.

Poster Ref: P1-H-006

Theme: H: Autonomic Nervous System

Degenerative changes in the mouse enteric nervous system during ageing.

M. Jill Saffrey[1], Frances M. Colyer[1], Heather A. Davies[1], Prasanna P.K.M. Gamage[1] and Richard N. Ranson[2]

[1]Open University, [2]Northumbria University, Newcastle-Upon-Tyne

The neurons of the enteric nervous system (ENS) play an essential role in the regulation of gastrointestinal (GI) functions. Evidence suggests that enteric neurodegeneration occurs during ageing and that some subpopulations of enteric neurons may be more vulnerable to degeneration than others. Enteric neurodegeneration is likely to contribute to GI dysfunction that is common in the elderly, for example, chronic constipation and faecal incontinence. Understanding how enteric neurons change during ageing is therefore important to inform development of potential treatments. We have previously shown that colonic motility is impaired in ageing C57/BL6 mice (Patel *el al.*, 2014). In addition, we found that both inhibitory myenteric motoneurons (nNOS-immunoreactive) and intrinsic primary afferent myenteric neurons (calbindin-immunoreactive) displayed degenerative changes in the ageing mouse distal colon, even though the total number of these neurons was maintained in aged animals (Gamage *et al.*, 2013). Here, we describe ultrastructural analysis of changes in myenteric neurons of the internal anal sphincter (IAS) muscle of mice. Animals were studied at 3-4, 24-25 and 30-32 months of age, by conventional electron microscopic techniques. Ganglia were sampled at regular intervals along the length of the IAS of each animal studied. All neurons and glial cells within each section were examined and quantitative analysis of organelles and other structures was performed. Results to date show an increase in the number of abnormal mitochondria, autophagic vacuoles and lipofuscin in neurons but not glial cells of aged animals. Other abnormal structures were also observed. These changes indicate that, in addition to possible neuronal loss in the ageing ENS, degenerative changes may result in neuronal dysfunction in the gastrointestinal tract.

This work was supported by the BBSRC Ageing Bladder and Bowel Initiative, Grant BB/G015988/1 to MJS & RNR.

References:

Patel *et al.* (2014) Impaired colonic motility and reduction in tachykinin signalling in the aged mouse. Exp.Gerontol., 53: 24-30.

Gamage P.P.K. *et al.* (2013) Myenteric neuron numbers are maintained in aging mouse distal colon. Neurogastroenterol. Motil., 25: e495-505.

Poster Session 2
Presented Monday 13 April 2015
Posters P2-A-001 to P2-G-014

Theme A: Development
Posters P2-A-001 to P2-A-020

Theme B: Molecular, Cellular and Synaptic Mechanisms
Posters P2-B-001 to P2-B-043

Theme C: Sensory and Motor Systems
Posters P2-C-001 to P2-C-031

Theme D: Learning, Memory and Cognition
Posters P2-D-001 to P2-D-061

Theme E: Sleep, Circadian and Neuroendocrine Mechanisms
Posters P2-E-001 to P2-E-017

Theme F: Nervous System Disorders
Posters P2-F-001 to P2-F-058

Theme G: Methods and Techniques
Posters P2-G-001 to P2-G-014

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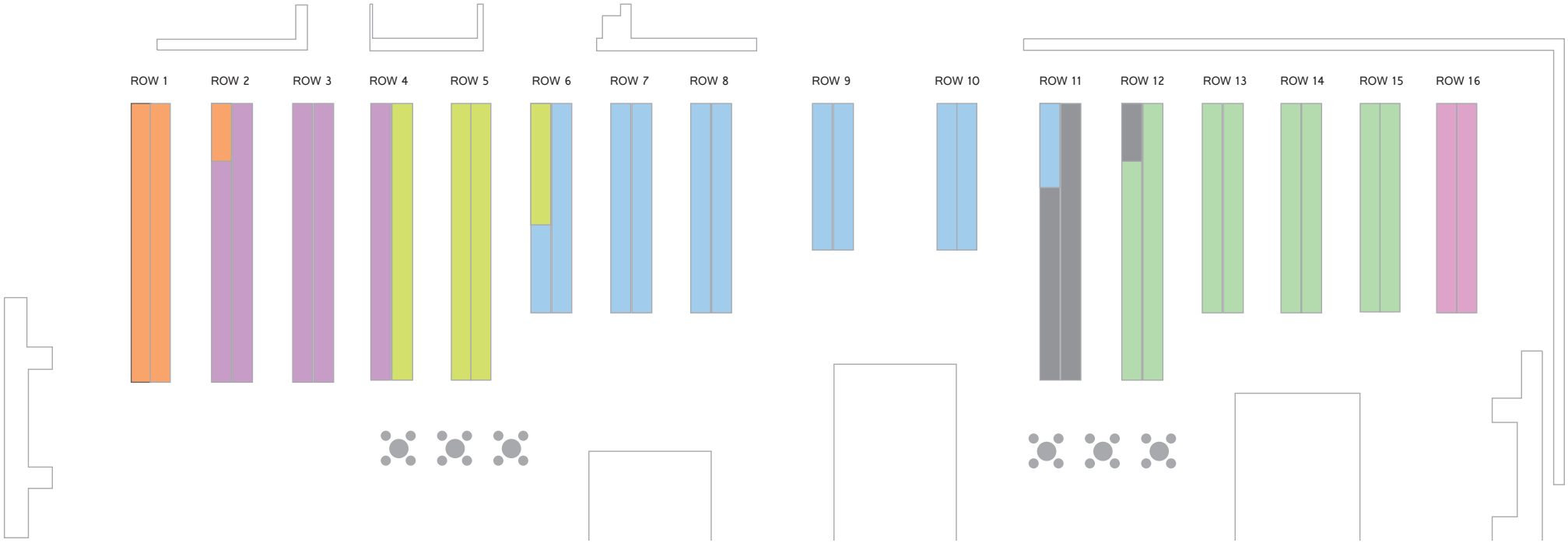


- A: Development
- B: Molecular, Cellular and Synaptic Mechanisms
- C: Sensory and Motor Systems
- D: Learning, Memory and Cognition
- E: Sleep, Circadian and Neuroendocrine Mechanisms
- F: Nervous System Disorders
- G: Methods and Techniques
- H: Autonomic Nervous System

Theme A: Development

Posters P2-A-001 to P2-A-020

Poster Ref: P2-A-001

Theme: A: Development

Identifying Pax6 targets in the developing neocortex.

Martine N Manuel, Zrinko Kozic, John O Mason and David J Price

University of Edinburgh

The neocortex, in evolutionary terms the newest part of the cerebral cortex, is the seat of higher cognitive functions. Its normal development requires the production, positioning and appropriate interconnection of very large numbers of both excitatory and inhibitory neurons. Pax6 is one of a relatively small group of transcription factors that exert high-level control of cortical development, and whose mutation or deletion from developing embryos causes major brain defects and a wide range of neurodevelopmental disorders. Pax6 is very highly conserved between primate and non-primate species, is expressed in a high rostro-lateral to low caudo-medial gradient throughout the developing cortex and is essential for normal corticogenesis. Our understanding of Pax6's functions and the cellular processes that it regulates during mammalian cortical development has significantly advanced in the last decade, owing to the combined application of genetic and biochemical analyses. However, we know less about the molecular mechanisms of Pax6 actions. The aim of our research is to further our understanding of the complete gene networks that Pax6 regulates. We used a tamoxifen inducible Emx1-cre transgene and a conditional Pax6 allele to specifically delete Pax6 from the cortex (Pax6cKO). Tamoxifen was administered to pregnant mice at E9.5 and embryos collected at E12.5 or E13.5. We collected control and Pax6cKO embryos and extracted RNA from the rostral cortex, which normally contains highest levels of Pax6, or the caudal cortex. Samples were then analysed by RNA sequencing (RNAseq). We used bioinformatics and experimental approaches to analyse the datasets. In particular, we found that a number of genes implicated in GABAergic differentiation pathways in the midbrain, cerebellum or spinal cord - such as Ptf1, Prdm13, Helt or Pax7 - were upregulated in the cortex of Pax6cKO embryos. (i) The RNAseq data suggest that a key role of Pax6 may be in regulating the balance between glutamatergic and GABAergic differentiation and (ii) the two timepoints give us the ability to begin to distinguish between direct and indirect effects of Pax6 and to begin to identify the network of genes controlled by Pax6 in the developing forebrain.

Poster Ref: P2-A-002
Theme: A: Development

The regulation of Notch ligands Dll1 and Jag1 during cortical development.

Elena Dora, Ian Simpson, John Mason and David Price
Edinburgh University

The regulation of gene expression resulting in the formation of the mammalian cerebral cortex is tightly regulated by a group of transcription factors. The deletion of any one of these transcription factors results in numerous defects whose nature and severity depends on the role of the transcription factor in the regulation of complex gene regulatory networks involved in development. There is currently relatively little knowledge about the gene networks that these transcription factors control and how they exert their regulatory effects.

The paired-box transcription factor Pax6 has been identified as a master regulator of gene networks involved in cortical development and its deletion results in numerous cortical defects such as an abnormally thin cortical plate and a vastly expanded proliferative zone. Previous work in our lab identified a list of candidate genes that are likely to be regulated by Pax6 in the developing cortex. Members of the Notch signalling pathway were potential Pax6 targets of particular interest since Notch signalling plays a crucial role in the maintenance of neural progenitor cells during development and consequently plays a critical role during corticogenesis.

Our work aims to identify the regulatory relationship between Pax6 and Notch ligands Dll1 and Jag1 during cortical development. Double label analysis of both gene and protein expression has provided insight into the relationship between Pax6 and Dll1 in progenitor cell subpopulations during cortical development. *In situ* hybridisation and qPCR results confirmed that loss of Pax6 causes loss of Dll1 expressing cells and downregulation of Jag1, indicating that both ligands are regulated by Pax6. Bioinformatic screening suggests that Jag1 is a likely candidate to be a direct target of Pax6. Ongoing work aims to confirm Jag1 as a direct target by visualisation of reporter gene expression produced by predicted enhancer elements driven by Pax6.

Poster Ref: P2-A-003

Theme: A: Development

Rapid neuroepithelial contractions expel damaged cells from the developing brain.

Leah Herrgen[1], Oliver Voss[2] and Colin Akerman[2]

[1]Centre for Neuroregeneration, University of Edinburgh, [2]Department of Pharmacology, University of Oxford

Background: Both developing and adult organisms need efficient strategies for wound repair and regeneration after injury. In adult mammals, wound healing is a lengthy and incomplete process which usually leads to loss of tissue function through scarring. In particular, the consequences of damage to the central nervous system of mammals are often devastating because their capacity to heal and regenerate the injured neural tissue is extremely limited. In contrast, embryonic wounds heal quickly and completely. Indeed, the developing brain can recover completely, even from major injury, within a few hours but how this is accomplished at the molecular, cellular and tissue level is not known.

Results: Using *in vivo* imaging in the developing brain of *Xenopus laevis*, we show that ATP is released from damaged cells after injury. The binding of ATP to P2X and P2Y purinergic receptors on neural progenitors triggers both long range calcium waves and an activation of the small GTPase Rho in these cells. This leads to a reorganisation of the actin cytoskeleton and an activation of the actomyosin contactile machinery, which induces rapid and pronounced apical-basal contractions of the neuroepithelium. These contractions drive the selective expulsion of necrotic cells into the brain ventricle within seconds of wounding. Successful cell expulsion prevents an exacerbation of the injury by averting the death of nearby cells.

Conclusions: The expulsion of damaged cells through neuroepithelial contraction contributes to the restoration of tissue integrity after injury and therefore represents a novel mechanism for rapid wound healing in the developing brain.

Poster Ref: P2-A-004

Theme: A: Development

The regulatory role of Pax6 on Cell Division Cycle Associated 7 protein and cortical progenitor cell proliferation.

Yu-Ting Huang[1], Da Mi[1], Katrin Ruisu[2], Asimina Pantazi[1], John Mason[1] and David Price[1]

[1]University of Edinburgh, [2]University of Tartu, Finland

Forebrain development is controlled by a set of transcription factors which are expressed in dynamic spatiotemporal patterns in the embryonic forebrain and are known to regulate complex gene networks. Pax6 is a transcription factor that regulates corticogenesis and mutations affecting Pax6 protein levels cause neurodevelopmental defects in eyes and forebrain in both humans and mice. In previous studies, it is shown that the graded expression pattern of Pax6 protein, which is high rostro-laterally to low caudo-medially in the cerebral cortex, is critical for its control of cell cycle progression and proliferation of cortical progenitors. However the underlying mechanisms are still unclear. Based on a microarray analysis, we identified a number of cell cycle-related candidate genes that may be affected by Pax6. One such gene, Cell division cycle associated 7 (Cdca7) is expressed in a counter-gradient against that of Pax6. In addition, Cdca7 mRNA expressions is upregulated in Pax6 null (Small eye) mutants and downregulated in mice that overexpress PAX6 (PAX77). There are several potential Pax6 binding motifs close to Cdca7 gene. One of them is proven to be physically bound by Pax6 *in vivo* by chromatin immunoprecipitation. Promoter luciferase assays using fragments combining four suspect binding motifs show that Pax6 is functionally critical. Cdca7 is a Myc and E2F1direct target and is upregulated in some tumours but its biological role is not fully understood. Current work using in utero electroporation to overexpress Cdca7 around the pallial-subpallial boundary (PSPB), where Cdca7 expression levels are normally lowest, to test the effects on the cell cycle of cortical progenitor cells in this region. In E12.5 mice embryos, overexpression of Cdca7 protein causes less proportion of Tbr2 positive cells, which represent the basal progenitor cells. This result implies that Cdca7 may affect cell fate decision during the cortical development.

Poster Ref: P2-A-005

Theme: A: Development

Involvement of a transient developmental interneuron circuit in the establishment of thalamocortical circuitry.

Daniel Lyngholm, André Marques-Smith, Jacqueline Stacey and Simon J. B. Butt

University of Oxford

GABAergic interneurons are important for the function of the cerebral cortex, serving to co-ordinate and synchronise activity. However, in contrast to understanding of the mature neocortex, the role of GABAergic interneurons (IN) in development is less well established. INs have been proposed play an important role in the generation of early synchronous activity and therefore are likely to be involved in circuit formation. We propose that the balance of specific sources of inhibition between distinct subsets of early born Nkx2-1–derived INs may have a critical role in the developmental synchronization of the cortical circuit mediating thalamocortical integration.

To test this hypothesis, we have mapped global or discrete emergent GABAergic input using laser-scanning photostimulation of either caged glutamate to drive global inhibition or caged ATP in a mouse line with conditional expression of a heterologous ATP receptor (P2X2) in distinct interneuron populations for conditional uncaging.

Focusing on thalamorecipient layer (L)4 of S1 barrel field of mouse cerebral cortex in the first two postnatal weeks, we show that glutamatergic spiny-stellate neurons (SSNs) in L4 initially receive both intra- and interlaminar (mainly L5b) global GABAergic input, but transition to an exclusively intralaminar input profile by the end of the critical period for thalamocortical plasticity. Mapping using conditional uncaging reveals that the initial interlaminar innervation is provided by a discrete population of L5b somatostatin-positive cells.

Finally, we demonstrate that the transition to exclusively local L4 GABAergic innervation requires sensory experience and that transient somatostatin IN interlaminar innervation can be perturbed by altering putative parvalbumin IN signalling through disruption of activity-dependent Neuregulin-ErbB4 signalling, leading to disruption to the normal development of thalamocortical innervation of L4.

Poster Ref: P2-A-006
Theme: A: Development

Serotonin enhances the development and adult regeneration of motor neurons in the spinal cord of zebrafish.

Karolina S. Mysiak, Antón Barreiro-Iglesias, Michell M. Reimer, Angela L. Scott, Yujie Yang, Thomas Becker and Catherina G. Becker
Centre for Neuroregeneration, University of Edinburgh

The unparalleled capacity of zebrafish to regenerate a lesioned spinal cord provides an exciting model for studying the re-establishment of neuronal circuitry after injury. In addition, embryonic zebrafish, due to their transparency, ease of access and rapid development offer the means for investigating the mechanisms of spinal cord development *in vivo*. Hence, spinal regeneration and development can be compared in the same species.

Previous research has shown that regenerative processes that replenish the motor neuron pool in the adult spinal cord after injury recapitulate some of the molecular events active during embryogenesis, for example sonic hedgehog, notch or dopamine signalling.

The purpose of the present study is to investigate the role of serotonin (5-HT) in development and adult regeneration of zebrafish spinal cord.

Firstly, we determined that supplementing embryos with an external source of 5-HT causes a surge in the production of motor neurons. We pinpointed multiple 5-HT receptors expressed by spinal motor neuron progenitor (pMN) cells, and using specific agonists and antagonists confirmed their contribution to the enhancing effects of 5-HT.

In adult spinal cord regeneration, we showed that treatment of the injured animals with 5-HT promotes an increase in the number of newborn motor neurons caudal to the site of the spinal lesion, where the descending 5-HT fibres from the brain have been lost. Conversely, ablating the 5-HT fibres with a specific toxin caused a reduction in motor neuron production rostral to the injury site. In addition, we showed that the adult pMN-like cells proliferated more in response to 5-HT after lesion. Interestingly, neither of the manipulations had an effect on the number of serotonergic spinal interneurons.

Overall, our results suggest that 5-HT acts as a positive signal for motor neuron production during development and regeneration, possibly through a direct action on progenitor cells.

The project is funded by the BBSRC, KSM is sponsored by a BBSRC DTG award, AB-I is sponsored by the Xunta de Galicia (Spain), AS by an EMBO long term Fellowship and YY is funded by a Charles Darwin Scholarship with a Gordon Lennie Bursary and an Edinburgh Global Research Award.

Poster Ref: P2-A-007

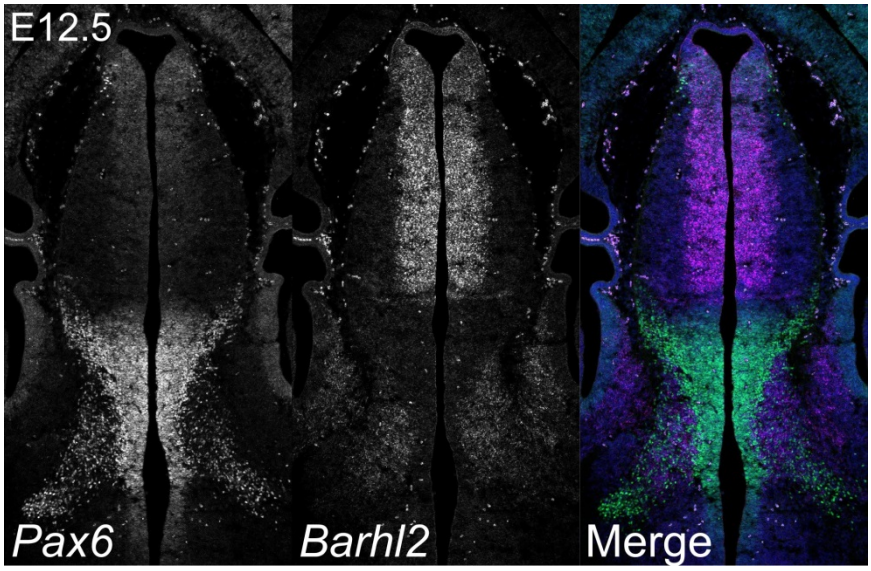
Theme: A: Development

Interactions between Pax6, Barhl2 and Shh in the control of diencephalic patterning.

Elisa Parish[1], John Mason[1], Tomomi Shimogori[2] and David Price[1]

[1]The University of Edinburgh, [2]RIKEN Brain Science Institute, Japan

The morphogen Shh controls many major patterning events of early diencephalic development. It is secreted from the diencephalon's organizing centre, the zona limitans intrathalamica (ZLI). The transcription factor Pax6 is required for the correct formation of the ZLI and also serves to modulate Shh transcription. More recently the transcription factor Barhl2 has been shown to be essential for the induction of the ZLI. There is evidence to suggest the existence of mutual transcriptional repression between Pax6 and Barhl2 and this may also play a role in diencephalic patterning. We have mapped and quantified the spatiotemporal dynamics of Pax6 and Barhl2 in order to investigate their potential interactions. We have also investigated their relationships with Shh by using drug treatment to block Shh activity and in utero electroporation to ectopically express Shh. We have used our findings to develop a new model for the control of ZLI development and its subsequent influence on diencephalic patterning.



Confocal images of a coronal section of the mouse diencephalon at embryonic day 12.5, treated with fluorescence immunohistochemistry for Pax6 protein and fluorescence *in situ* hybridisation for Barhl2 mRNA. The largely complementary expression of both transcription factors can be seen along with their expression along opposing gradients within the developing thalamus.

Poster Ref: P2-A-008

Theme: A: Development

Delayed cerebellar development as a result of *in utero* androgen hyper-exposure.

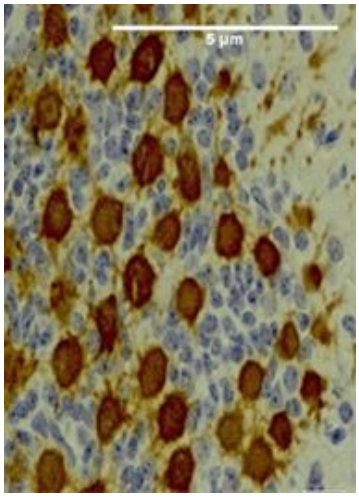
Claire Garden and Lisa-Marie Wilson

Edinburgh Napier University

It is widely acknowledged that fetal programming by steroid hormones of endocrine organs impacts on reproductive and metabolic health in later life. Steroid hormones also play a major role in the development of the CNS with those brain areas involved in sexual behaviour having been the focus of most neuroendocrine studies to date i.e. the hypothalamus and pituitary gland. This occurs *via* intracellular and cell-surface receptors that regulate changes in protein synthesis to modify events related to neuronal survival and synapse formation.

The cerebellum is known to express many of the proteins required to respond to, and synthesise, steroid hormones, and therefore is a potential target for their fetal programming effects. Furthermore, cerebellar pathology is associated with neurodevelopmental disorders such as Autistic Spectrum Disorder and Schizophrenia. An ovine steroidal fetal programming model was utilised to investigate how gene expression in the male cerebellum is affected by androgen exposure during development, and also to examine the resulting changes in male cerebellar architecture.

The main aims of this study were to 1. Identify changes in the cerebellar expression of steroid pathway genes, using quantitative real-time polymerase chain reaction (qRT-PCR), that result from exposure to prenatal excess androgen (2x20mg depot injections at Gestational Day 62 and GD 82 of testosterone propionate (TP)) in GD90 male sheep, and 2. Identify changes in Purkinje cell number, size and shape that result from treatment using histology. We show that mRNA levels of progesterone receptor and steroid acute regulatory protein (the rate-limiting step for steroidogenesis) are altered as a result of androgen, but not estrogen, treatment in males. Furthermore, we also demonstrate that androgen, but not estrogen, over-exposure delays cerebellar development in these males, which may have consequences in later life.



Calbindin staining of the Purkinje cell layer in the Testosterone Propionate treatment group of an ovine fetal programming model (gestational day 90). Where we observe a normal Purkinje cell layer one cell thick with well-developed processes and a unipolar apical dendrite, the treated group have a thicker, less well developed layer reminiscent of earlier gestational time points.

Poster Ref: P2-A-009
Theme: A: Development

Effects of nitric oxide on the development of cortical cultures.

Volko Straub and Yewande Okunoren-Oyekenu
University of Leicester

Nitric oxide (NO) has been recognised as an important signalling molecule within the nervous system that has wide ranging effects on cellular and synaptic properties. In addition to acute modulation of neuronal and synaptic activity, NO has also been shown to affect neuronal development and neuronal growth. For example, we have previously demonstrated that NO promotes neurite extension following axonal injury in the pond snail (Cooke *et al.*, 2013). In contrast, the situation in vertebrates and mammals is less well understood. Various studies have shown that NO synthase is strongly expressed during critical periods of mammalian CNS development suggesting that NO production is important for neurodevelopment. However, the precise nature of this role is not clear and contradictory effects have been reported in the literature.

In order to gain a better understanding of the role of NO in cortical development, we used primary cultures of dissociated cortical cells as a model system. The aim of our study is to characterise the effects of endogenous NO production and NO donor application on the development of cortical cultures, neurite growth and synapse formation. For this purpose, mixed cortical cultures containing both neuronal and non-neuronal cells were prepared from neonate rat pups on postnatal day 0-1. Cultures were treated chronically with either the nNOS inhibitor 7NI (1μM) or the NO donor DETA/NONOate (100μM) starting on day three of cell culture. Stock solutions of DETA/NONOate and 7NI were prepared in NaOH and DMSO respectively and treatments with NaOH and DMSO at equivalent concentrations served as controls. After 14 days, imunocytochemistry methods were used to stain for microtubule-associated-protein-2 (MAP-2), synaptophysin and GAD-65.

Here we show that blocking endogenous NO production has no apparent effects on the development of cortical cultures, whilst exogenous NO application has a concentration dependent effect on total cell number and the number of neurons, but no significant effect on the growth of surviving neurons. This suggests that NO can affect neuronal survival, possibly as a secondary effect due to effects on non-neuronal cells that support neuronal development.

Cooke et al (2013) The Journal of Neuroscience, 33 (13): 5626-5637.

Poster Ref: P2-A-010

Theme: A: Development

Characterising the high mobility group nucleosome-binding proteins (HMGNs) during neuronal differentiation of mouse P19-embryonic carcinoma stem cells in a defined adherent culture system.

Abdulmajeed Sindi, Sylvia Garza-Manero, Erick Carvalho Mendez and Katherine L. West

Institute of Cancer Sciences, University of Glasgow

Embryonic stem cells (ESCs) possess the properties of self renewal and pluripotency, and represent a potentially unlimited source of defined cells for cell transplantation therapy. Embryonic carcinoma cells (ECCs), which are malignant cells derived from teratocarcinomas and originate in gonads and extragonadal sites, have also been found to resemble ESCs in their features. When mouse ECCs and ESCs are sited in a blastocyst, both can play a role in embryonic development and contribute to normal tissues, resulting in a chimeric embryo. Neuronal induction can be accomplished *in vitro* when undifferentiated ESCs or ECCs are stimulated by retinoic acid in the absence of serum. Different protocols for neural induction of P19 cells have been used for deriving neurons, astrocytes, microglias and oligodendrocytes. Recently, Nakayama *et al* (J Neurosci Methods, 2014, 227:100-6), developed a method for rapid neural induction that efficiently induces P19 cells to differentiate into neurons within four days, by-passing the need for embryoid body formation. We used this method for characterising high mobility group nucleosome-binding proteins (HMGNs) during neural differentiation.

HMGN family members are nucleosome-binding proteins that modulate chromatin structure and regulate DNA replication, DNA repair, and gene expression. Detailed studies have shown that the expression level of HMGN proteins is tightly related to differentiation in both Xenopus and mice. Furthermore, the expression of HMGN1 and HMGN2 must decrease during erythropoiesis, chondrogenesis, and myogenesis in order to ensure proper differentiation. Data from the Allen Brain Atlas indicates that HMGN1 and HMGN2 mRNA is highly expressed in neural stem and progenitor cells during brain development, with greatly reduced expression in regions of the brain containing terminally differentiated neurons. Here, we demonstrate that the expression of HMGN1 and HMGN2 proteins gradually decreases upon terminal differentiation of neurons *in vitro*, until less than 10% of the original protein level remains. This adherent culture system thus provides a model to investigate the role of HMGN proteins and epigenetic processes during neuronal differentiation.

Poster Ref: P2-A-011

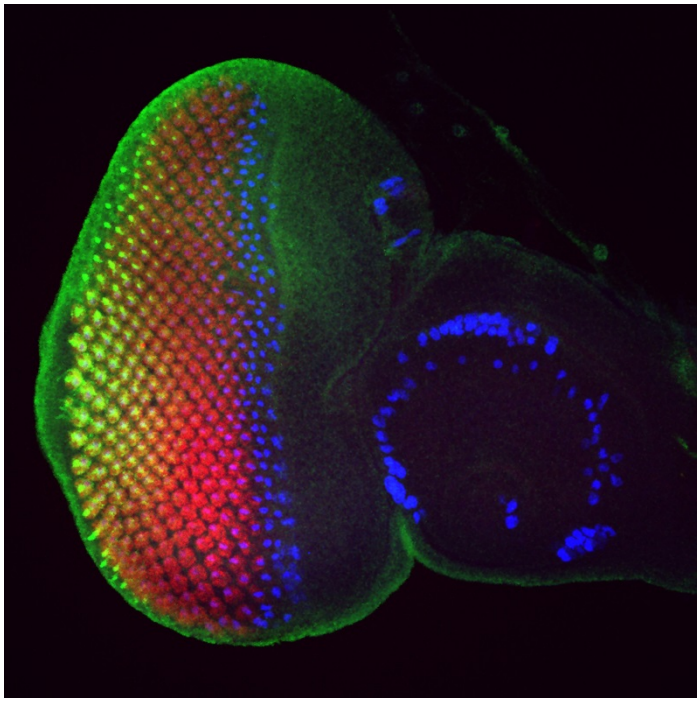
Theme: A: Development

Characterising the role of the novel neurogenic mTOR pathway gene unkempt in the *Drosophila* central nervous system.

Katja T. Maierbrugger and Joseph M. Bateman

Wolfson Centre For Age Related Diseases, King's College London

The timing of neurogenesis is critical to produce a complete and fully functional nervous system. One important timing regulator is the mechanistic target of rapamycin (mTOR) signalling pathway. The mTOR kinase integrates signals from mitogens, nutrients and energy levels to regulate growth, metabolism and also neurogenesis in both *Drosophila* and mammalian model systems. Mutations in essential components of this pathway can alter the timing of neurogenesis and may contribute to diseases such as epilepsy and autism. We have previously shown that the insulin receptor (InR)/mTOR pathway plays a key role in regulating the timing of photoreceptor differentiation in the developing *Drosophila* eye. We recently showed that the gene unkempt (unk) is a novel negative regulator of photoreceptor differentiation that acts downstream of mTOR in the *Drosophila* eye (Avet-Rochex *et al.*, 2014). Unk is a zinc finger/RING domain protein that has been shown to be involved in ubiquitination and to physically interact with mTOR in *in vitro* studies. In this project *Drosophila* is used as a model system to test whether unk regulates the differentiation of neural stem cells in the CNS. We find that Unk is strongly expressed in neuroblasts and neurons in the *Drosophila* larval brain. Overexpression of Unk, together with its binding partner Headcase (Hdc), causes a significant reduction in the number of neuroblasts in the larval brain, indicating a potential role for Unk in neurogenesis in the *Drosophila* CNS. Furthermore, we are investigating the mechanism by which mTOR physically interacts with and regulates Unk and are analysing specific phosphorylation sites in Unk and their potential effect during neuronal differentiation. The results of these studies, as well as analysis of potential new binding partners of Unk will be presented.



Drosophila eye disc stained for differentiation markers.

Poster Ref: P2-A-012
Theme: A: Development

Late maternal folate supplementation rescues from methyl donor deficiency-associated brain defects by restoring microRNA pathways.

Andréa Geoffroy, Racha Kerek, Grégory Pourié, Déborah Helle, Jean-Louis Guéant, Jean-Luc Daval and Carine Bossenmeyer-Pourié
INSERM U954 – NGERE, Faculté de Médecine, Vandoeuvre-lés-Nancy, France

Dietary methyl donors, such as folate (vitamin B9) and vitamin B12, are centerpieces of one-carbon metabolism. Deficiencies lead to impairments of epigenetic mechanisms involving transmethylation reactions. Their prevalence in pregnant women warrants the public health strategy of periconceptional folate supplementation to prevent *in utero* growth retardation, neural tube defects (NTD) and other neurodevelopmental anomalies.

We showed that methyl donor deficiency during gestation in a rat model (Blaise *et al.*, 2007) as well as in H19-7 neuronal progenitor cells (Akchiche *et al.*, 2012) induces altered expression of some microRNAs such as let-7, miR-34, miR-124 and miR-137, with deleterious consequences on targets involved in the regulation of developmental and maturational processes of the central nervous system (Trim 71, Notch, Stat 3 and NMDA/AMPA) (Kerek *et al.*, 2013).

Folate supplementation at a daily dose of 3 mg/kg in pregnant rats from embryonic day 13 (E13) to E20, prevents or significantly reduces developmental abnormalities consecutive to methyl donor deficiency: NTD such as spina bifida, cerebellar and interhemispheric suture defects, brain growth retardation and atrophy of selective cerebral layers. This occurs at least partly through restoration of miRNAs expression and improvement of their related signaling pathways in deficient offspring.

In addition to anatomical benefits, folate supplementation during the third week of gestation and until weaning (postnatal day 21) was associated with better locomotor properties and improved learning capacities and memory in rat pups exposed to early methyl donor deficiency as compared to non-supplemented deficient offspring.

In conclusion, we showed that gestational deficiency in methyl donors was linked to various developmental defects in rat pups, in line with improper brain expression of a panel of microRNAs. Whereas it cannot fully prevent early-occurring NTDs such as spina bifida, maternal supplementation with folate during the period corresponding to the last trimester of pregnancy in women appeared to help preserve a normal development.

Poster Ref: P2-A-013

Theme: A: Development

Investigation of the relationship between aggregated alpha-synuclein and mitochondrial function.

Amy Reeve[1], Marthe Ludtmann[2], Plamena Angelova[2], Eve Simcox[1], Mathew Horrocks[3], David Klinerman[3], Sonia Gandhi[2], Doug Turnbull[1] and Andrey Abramov[2]

[1]Wellcome Trust Centre for Mitochondrial Research, Newcastle University, [2]Department of Molecular Neuroscience, Institute of Neurology, University College London, [3]Department of Chemistry, University of Cambridge

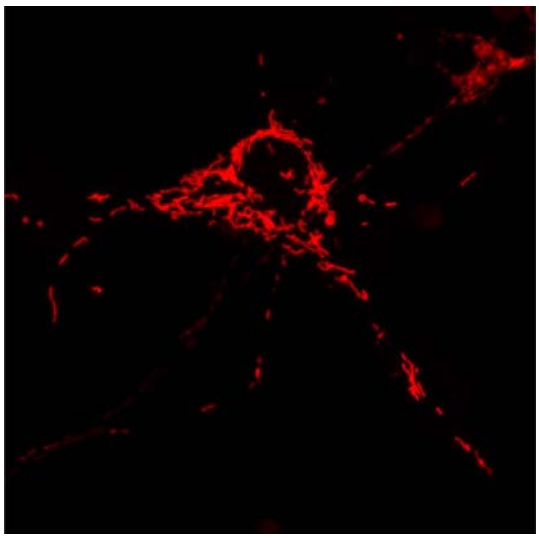
Objective: To investigate the relationship between aggregated forms of alpha-synuclein and mitochondria and the effect of such an interaction on mitochondrial function and cell survival.

Background: Alpha-synuclein is thought to be important for the modulation of dopamine signal at the synapse and upon damage becomes misfolded forming oligomeric and fibrillar forms. These altered forms of alpha-synuclein have been proposed to interact with membranes and organelles (including mitochondria) and are thought to have differential toxicities. Several studies have proposed that the interaction between alpha-synuclein and mitochondria causes mitochondrial dysfunction that may contribute to the pathogenesis of Parkinson's disease.

Methods: In order to investigate this interaction further we treated mouse embryonic cybrid stem cells and neurons which harboured complex I and IV defects with aggregated alpha-synuclein. We monitored the effect of each form of alpha-synuclein on various parameters of mitochondrial function including mitochondrial membrane potential, respiratory capacity, ATP and ROS production and cell death.

Results: We found that aggregated alpha-synuclein inhibited mitochondrial complex I, in the same way as pathogenic mitochondrial DNA mutations, within the control and complex IV deficient cells. The presence of an inherent defect in mitochondrial complex I did not exacerbate the effects of alpha-synuclein or lead to increased cell death. This would suggest that since complex I deficient cells have already adapted to their mitochondrial defect, the subsequent toxic effects of alpha-synuclein are reduced. Control cells and those with a complex IV defect were however more sensitive to the toxic effects of aggregated alpha-synuclein.

Conclusions: These data shed light on the effect of aggregated forms of alpha-synuclein on neurons harbouring different mitochondrial defects and gives insight into how these two processes may affect the survival of neurons within the substantia nigra.



We studied the effect of aggregated alpha-synuclein on mitochondria and mitochondrial function in live cells.

Poster Ref: P2-A-014

Theme: A: Development

Investigating whether disrupted placental function leads to alterations in maternal brain: part 1.

Hugo Creeth, Simon Tunster, Jessica Eddy, Anthony Isles and Rosalind John

Cardiff University

Objectives: During pregnancy, many changes take place in the mother including increased maternal forebrain neurogenesis and the induction of maternal behaviour. Studies in rodents suggest the possibility that endocrine signals originating from the placenta may play a role in inducing maternal behaviours. Here, we sought to test this hypothesis directly by genetically manipulating a key endocrine lineage of the mouse placenta.

Methods: Using a mouse model in which the spongiotrophoblast was disrupted by a genetic modification of the imprinted gene Phlda2, we investigated the theory that aberrant placental signalling results in alterations in maternal behaviour. Three cohorts of wild type dams carrying fetuses that possessed either a 50% reduction in the spongiotrophoblast (Phlda2 TG) or a 200% increase (Phlda2 KO) were generated using recipient embryo transfer (RET) and their behaviour was studied.

Results: Distinct changes in pup retrieval and nest building behaviour were observed, alongside differences in anxiety, assessed using the elevated plus maze (EPM) assay. Specific brain regions and placental samples were subject to microarray analysis to examine gene expression. A number of genes, and one gene family, were significantly altered in relation to WT mothers with a particular genotype litter.

Conclusions: This work provides the first experimental evidence that the fetal Phlda2 gene acts on the mother to stimulate maternal behaviours ensuring improved survival of the fetus when it is born. Translated into the human condition this work has relevance to postnatal depression, a disorder that affects 10-15% of pregnancies. Future directions of this work could offer a new approach to understanding such debilitating maternal mood disorders, which may originate in placental abnormalities, providing the potential for generating new therapeutics.

Future Directions: The future of this project is to look at the potential affect this maternal behavioural changes may have on the offspring's behavioural outcomes across the genotypes. We are currently in the process of identifying any changes in brain structure and neurogenesis in the maternal brains using immunohistochemistry.

Poster Ref: P2-A-015

Theme: A: Development

Investigating whether disrupted placental function leads to alterations in maternal brain: part 2.

Rosie Little, Hugo Creeth, Jessica Eddy, Simon Tunster, Rosalind John and Anthony Isles

Cardiff University

Pregnancy involves numerous changes for the mother in terms of physiology and behaviour. The brain of the mother undergoes multiple changes during this time which are, in part, programmed by the fetus *via* the placenta. We used a mouse model to investigate molecular differences arising in key regions of the maternal brain as a consequence of abnormal expression of the imprinted gene Phlda2 in the placenta. Phlda2 encodes pleckstrin homology-like domain family a member protein 2, and loss and over-expression of this gene alters the spongiotrophoblast cell lineage in the mouse placenta.

Wild-type (WT) dams were carrying fetuses that were either WT, Phlda2 knock-out, or over-expressing Phlda2 via a bacterial artificial chromosome (BAC) transgene. These females were allowed to litter and were also tested for changes in maternal behaviour ("Investigating Whether Disrupted Placental Function Leads to Alterations in Maternal Brain: Part 1") before being culled at P7. Here, we examine changes in maternal brain gene expression in a number of key regions including the hypothalamus and hippocampus. Target genes were identified by a previous microarray study, and were assessed in maternal brain here using quantitative PCR (qPCR). We are now examining whether the changes in maternal behaviour and brain gene expression also has consequences for the physiology and behaviour of the offspring.

Poster Ref: P2-A-016

Theme: A: Development

Automated tractography using TRACULA for the investigation of white matter tracts in patients with temporal lobe epilepsy.

Barbara Kreilkamp[1], Bernd Weber[2,3], Mark Richardson[4] and Simon Keller[1,4]

[1]Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, [2]Department of NeuroCognition/Imaging, Life&Brain Research Center, Bonn, Germany, [3]Department of Epileptology, University of Bonn, Germany, [4]Department of Clinical Neuroscience, Institute of Psychiatry, King's College London

Introduction: Diffusion Magnetic Resonance Imaging (dMRI) is not routinely used for clinical investigations of patients with temporal lobe epilepsy (TLE) [1]. One reasons for this is that clinical utility has not yet been evaluated. Our aim was to implement important pre-processing/analysis steps to avoid biasing of FA value estimation through anatomical mis-alignment/motion and to evaluate fractional anisotropy (FA) alterations of reconstructed white matter (WM) tracts known to be affected in patients with TLE.

Methods: MR scans had been previously acquired for 32 healthy controls, 18 left TLE (lTLE) and 15 right TLE (rTLE) patients [2].

Each participant received 3D T1/T2 weighted and dMRI scans [2], which were used for pre-processing and subsequent analysis. For each subject we performed automated cortical/subcortical segmentations of T1 data *via* Freesurfer [3]. The mean dMRI b0 image was co-registered to the T2 anatomical using Slicer [4]. Then the default TRACULA [5] pipeline was applied. We investigated FA values for six WM tracts: uncinate fasciculus (UF); inferior longitudinal fasciculus (ILF); superior longitudinal fasciculus, temporal (SLFt) and parietal (SLFp) segments; cingulum angular bundle (CAB); and anterior thalamic radiation (ATR).

Results and Discussion: Mean translational/rotational motion parameters were not significantly different between rTLE, lTLE and controls as determined by One-Way ANOVA for translation $F(N=64,62)=0.2$, $p=0.82$ and rotation $F(N=64,62)=0.11$, $p=0.89$, ruling out possible biases on FA values due to differences in motion.

Our results corroborate healthy controls' FA values reported for TRACULA [5]. Furthermore we found significantly decreased patient FA in tracts that survived Tukey correction after One-Way ANOVA (Figure 1), thus replicating previous results which used automated [6] and manual techniques [7].

Conclusion: We show that TRACULA is sensitive enough to detect previously published FA abnormalities in TLE and therefore might provide fast, reproducible assessment of WM tract properties in clinical settings.

References

[1] Keller *et al.* E 2014 [2] Keller *et al.* PO 2012 [3] Fischl NI 2012 [4] Johnson *et al.* IJ 2007 [5] Yendiki *et al.* FNI 2011 [6] Scanlon *et al.* JN 2013 [7] Thivard *et al.* NI 2005.

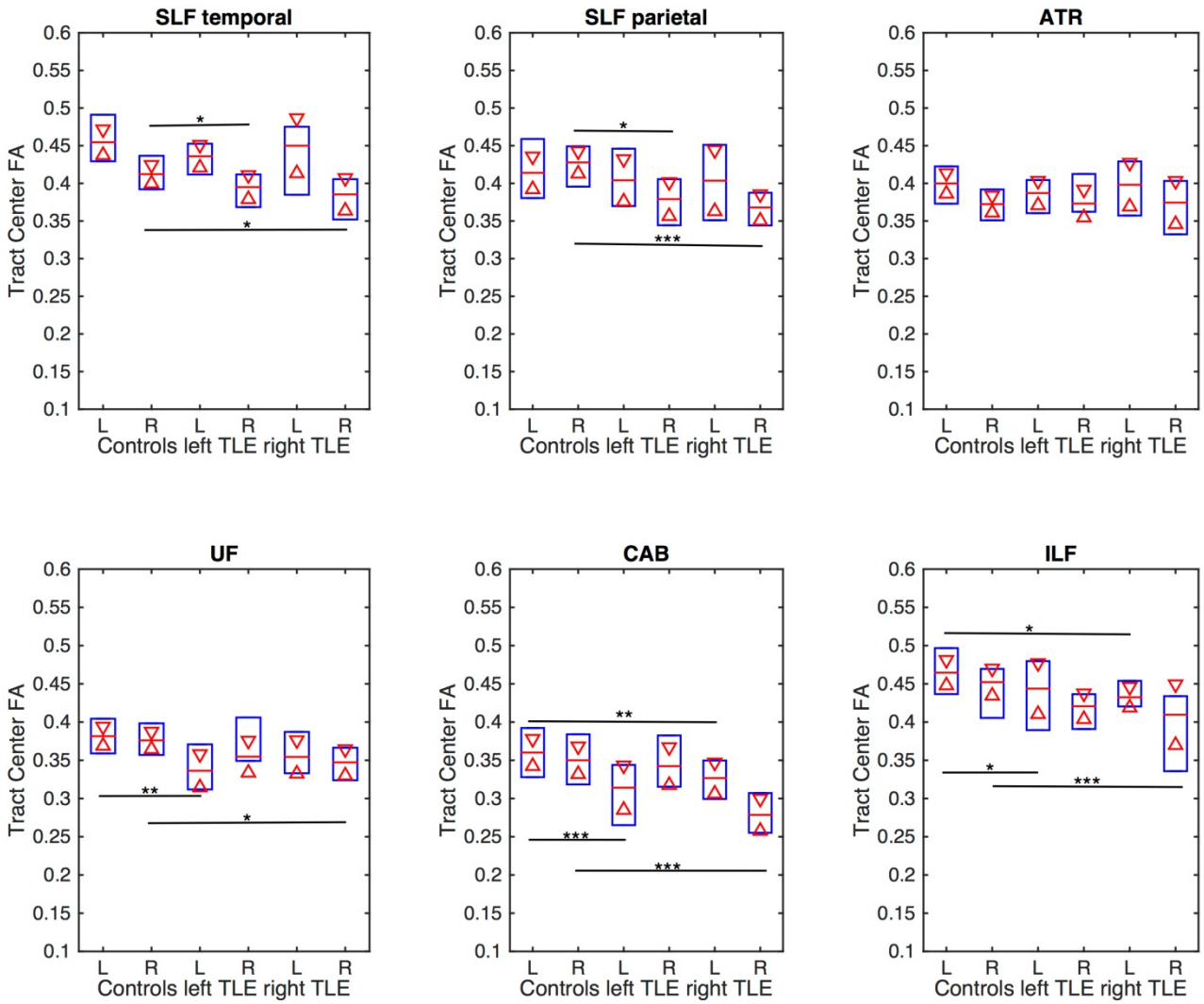


Figure 1. TRACULA ROI FA in SLFt, SLFp, ATR, UF, CAB, ILF.

Distributions plotted for left/right tracts of controls, lTLE, rTLE. Box edges mark 75th/25th percentiles, line represents median, triangles indicate 95% confidence intervals. Differences are marked, ipsilateral below, contralateral above boxes.

N: 32 controls, 18 lTLE, 15 rTLE

*0.05>p>0.01;**0.01>p>0.001;***p<0.001

Poster Ref: P2-A-017

Theme: A: Development

Nonlinear growth: an origin of hubs in complex networks.

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Highly connected nodes or hubs are observed across a wide range of complex networks, in particular neural networks. Their degree is higher than expected from regular, random networks. Interestingly, hubs often tend to preferentially connect with one another, rather than lower-degree nodes, giving rise to rich-club organization. The peculiar structural connectivity of hubs also entails a central role in the functioning of the overall network. For example, hub regions in the human brain have been shown to be central in brain communication and neural integration (van den Heuvel and Sporns, 2013). Therefore, shining light on the developmental process of hub formation is a crucial step towards understanding network functionality in general. In this work, we propose a novel and biologically plausible model that accounts for hub-related network properties, and compare its performance with preferential attachment and duplication-divergence models. For this assessment we use different real-world datasets including chemical synapses in *Caenorhabditis elegans* and axonal connections between brain regions in the rhesus monkey (macaque).

Poster Ref: P2-A-018
Theme: A: Development

Direct interactions between Gli3, Wnt8b and Fgf signalling underlie dorsal telencephalic development.

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Patterning of the dorsal telencephalon is critically dependent on a complex network of interactions between intercellular signalling molecules and transcription factors (TFs). Several signalling molecules including Fgf8, several Wnts and Bmps act as morphogens to determine dorsal telencephalic cell fates. In addition, transcription factors are involved in regulating fate determination of cortical progenitors and their proliferation and differentiation. Individual roles of these signalling molecules and TFs have been extensively studied, but very little is known how these molecules interact to control dorsal telencephalic patterning.

The Gli3 zinc finger TF as a downstream effector of Sonic hedgehog (Shh) signalling is a key regulator of telencephalic development. Gli3 also regulates the expression of Fgf8/15/17/18 and of Wnt7b/8b. Our analysis of Gli3 mutant mice further demonstrated that a tight balance between Gli3, Fgfs and Wnts is not only crucial for patterning but is also required for controlling the development of the corpus callosum, however, the molecular basis for these interactions remains largely unknown. Here, we investigate the hypothesis that Wnts, Fgfs and the Gli3 TF directly regulate each other's expression. We show that a Wnt8b telencephalon enhancer contains a binding site for Ets TFs which are involved in Fgf signalling. Mutation of this site results in increased expression of a lacZ reporter gene in transgenic mice. In turn, a binding site for the Tcf transcription factor involved in Wnt/b-catenin signalling is required to repress the activity of an Fgf17 forebrain enhancer. Moreover, we show that the activity of the Gli3 dorsal telencephalon enhancer depends on Fgf signalling. Mutations of an Ets binding site within this enhancer abolish its activity in the dorsomedial telencephalon. Interestingly, this flanks a Tcf binding site which we previously showed to be essential for Gli3 enhancer activity and the presence of Etv4 protein increases the binding of Lef1 to the Gli3 enhancer. Overall, these findings suggest direct interactions between Gli3, Wnt8b and Fgf17 including reciprocal negative interactions between Wnt and Fgf signalling and a cooperative interaction between these signalling pathways to regulate Gli3 expression.

Poster Ref: P2-A-019

Theme: A: Development

The effects of early testosterone exposure on microglia in the rat cerebellum.

Godwin Tong[1], Martina Rodie[2], David Russel[1], Mhairi Macrae[3], Peter O'Shaughnessy[4], Faisal Ahmed[2] and Michelle Welsh[1]

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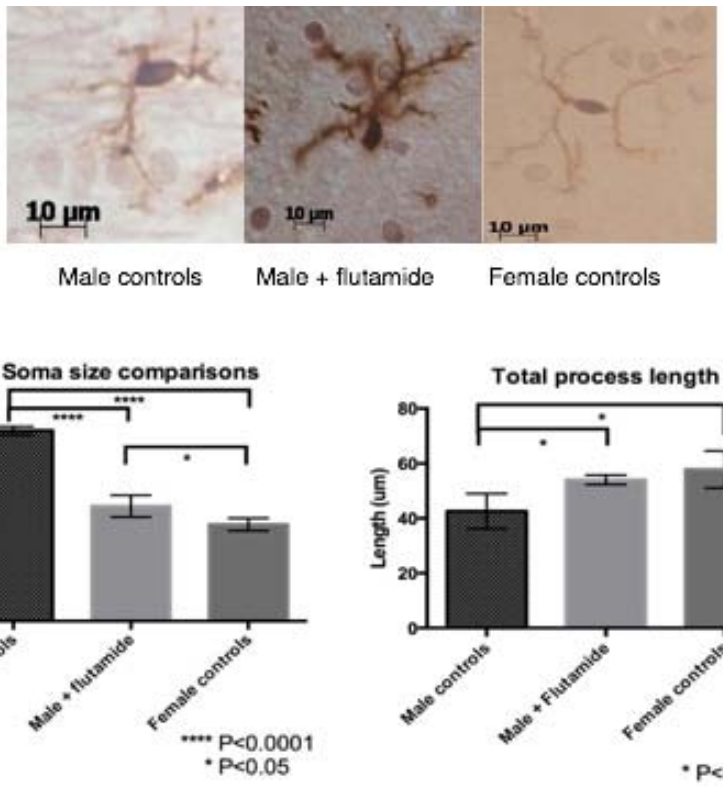
Throughout male human development, distinct peaks of androgen levels are reported during mid pregnancy, at birth and during puberty. The exposure of the brain to various androgens plays a role in the complex sexual differentiation of the male brain. Sexual dimorphisms in brain regions such as the hypothalamus are well documented. However, sex differences in the cerebellum are less well understood and equivocal, despite cerebellar related neuropsychiatry disorders such as autism and schizophrenia appearing to affect males in a biased manner.

Recently, a study revealed sex-specific cellular differences in microglia in the murine preoptic area (POA). More importantly they described a novel role of microglia in driving the masculinisation effect of estradiol in the POA and are essential for characteristic male mating behaviour. The question remains as to whether similar cellular dimorphisms exist in the cerebellum, and if so, whether these might have implications on cerebellar function. We therefore hypothesise that sexual dimorphisms exist within the cellular structures of the cerebellum and are induced by androgens during early post-natal life.

In this study we performed histological characterisation of microglia within the cerebellum of male and female rats (aged 10 weeks) as well as males exposed to the androgen receptor antagonist flutamide, during post-natal days (PN) 1–5. We show that sexual dimorphisms of the cerebellum exist in healthy adult rats, with regards to microglia cell numbers, size, and process length ($P < 0.005$, $P < 0.0001$ and $P < 0.05$ respectively). Blocking of early post-natal testosterone action in males prevented this masculinisation of microglia, resulting in a female-like phenotype. Taken together, these data support the hypothesis that the cerebellum is sexually dimorphic and androgen action during PN1-5 is responsible, at least in part for these differences. To our knowledge, this the first report of sexual differences in cerebellar microglia and further work is needed to establish if these early life hormonal alterations translate to later life behavioural differences. Understanding the effect of early testosterone exposure has on the brain may help to develop pharmaceutical or behavioural based interventional strategies in the future.



Microglia representative of male and female control rats, as well as male rats treated with flutamide. Adult male controls had larger and more microglia in the cerebellum whereas females had microglia with longer process length. Treatment with flutamide during PN1-5 prevented this masculinisation of microglia, resulting in a phenotype more similar to that of control females than males.

Poster Ref: P2-A-020

Theme: A: Development

Brain function after long term zolpidem in a patient with traumatic brain injury.

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Zolpidem is known to transiently improve neurological disability after brain damage, and to reverse Disorders of Consciousness such as the Vegetative and Minimally Conscious States. Repeat 99mTcHMPAO SPECT scans were used to monitor cerebral perfusion in a fully conscious, long term neurologically disabled ex- coma patient, years after a traumatic brain injury. 18F-FDG and 11C-Flumazenil hybrid PET scans were used to image cerebral metabolism and benzodiazepine receptor function, and CT and MRI scans to image anatomical integrity of the brain. Here we present results and show a permanent improvement in the patient's neurological and brain function after four years of daily zolpidem treatment, in addition to daily transient improvements.

Theme B: Molecular, Cellular and Synaptic Mechanisms

Posters P2-B-001 to P2-B-043

Poster Ref: P2-B-001

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Directional migration of oligodendrocyte precursor cells in response to injury: discovery and validation of novel candidate factors.

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Regeneration of the adult Central Nervous System requires the reconstruction of the myelin sheath by new oligodendrocytes derived from oligodendrocyte precursor cells (OPCs), the resident glial stem cells of the CNS. Following demyelination, secreted chemomigratory factors released at the injury site form gradients which pervade the CNS tissue activating and guiding OPCs to lesion sites. However, this process in inefficient in humans leading to the progressive axon loss observed in Multiple Sclerosis and contusion spinal cord injury. One reason for this inefficiency is a lack of OPC migration into injury sites.

To identify possible migratory factors for OPCs released at lesion sites, we interrogated gene expression microarray data from whole lesion sites in two demyelinating injury types in rats, demyelination in the brain using lysophosphatidylcholine and contusion spinal cord injury.

In both data sets, we identified genes most upregulated at timepoints associated with OPC infiltration into lesion sites by fold filtering and refined this list by selecting secreted factors using the ensembl biomart tool. We identified the expression signatures of known migratory factors for OPCs and used correlation analysis to find secreted factors with similar expression patterns. Gene ontology enrichment was used to identify candidates active in migration associated pathways for further analysis. The candidate list was then refined by verification of novel receptor expression in OPCs by RT-PCR and IF.

We have screened for the chemomigratory effect of suitable candidate factors using the X-celligence cell invasion/migration system (ACEA Biosciences). This system adapts the conventional Boydon chamber assay, but incorporates 80% coverage of the lower membrane with electrodes which measure electrical impedance, giving accurate real time quantification of cells directionally migrating towards a candidate factor and eliminating the necessity for microscopy and quantification.

Using this approach, we have successfully identified 4 novel factors for action on OPCs : 2 proliferative, 1 chemorepellant and 1 chemoattractant. We are testing these novel factors in our models to determine the mechanisms of the early regenerative response in the CNS to injury.

Poster Ref: P2-B-002

Theme: B: Molecular, Cellular and Synaptic Mechanisms

The effects of induced oncogenicity on microglia activity in zebrafish.

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University of Edinburgh

The externalization and redistribution of phosphatidylserine (PS) onto the outer surface of the plasma membrane expressed on apoptotic cells is widely acknowledged as the key “Eat-Me” recognition ligand in neuronal phagocytic pathways and a main marker for cellular apoptosis. This upregulated PS exposure has since been demonstrated in cancer studies, where oncogenic cells express for elevated levels of surface PS co-localization. However, these cells show for a high propensity to evade phagocytosis and avoid cell death. In the present study, the apoptotic properties of oncogene-induced (Akt1, EGFRvIII, HRasV12) PS exposure and the physiological behaviours of microglia to overexpressed oncogenicity were determined through a series of live imaging carried out on embryonic zebrafish (*Danio rerio*) brains *in vivo*. Following the incubation with Acridine Orange (AO) to identify apoptotic cells, it was found that oncogenic cells co-expressed for PS labelling were not stained for AO; suggesting that oncogene-induced PS exposure is not a marker for cellular apoptotic nature. Through time-lapse imaging carried out, it was further observed that neuronal microglia were highly activated and motile following oncogenic overexpression; suggesting for an affected balance within the microenvironment and corresponding microglia active states in response. Furthermore, video analyses demonstrate for the interesting yet unpredictable nature of oncogenic-phagocytic interactions; in contrary to earlier beliefs, findings suggest that surface PS exposure only plays a relative role in programmed phagocytic removal. Taken together, preliminary results suggest for a complex relationship existing between oncogenic cells and neuronal phagocytes involving the balance between PS expression in concert with other recognition ligands.

Poster Ref: P2-B-003

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Effect of beta amyloid peptide on CA1 pyramidal neuron: a sodium and potassium conductances based model study for possible treatment.

Chitaranjan Mahapatra and Rohit Manchanda

Indian Institute of Technology Bombay

Evidence from a number of independent studies has demonstrated that generation of pathogenic β- amyloid (Aβ) peptides, one of the characteristic hallmarks of Alzheimer's disease (AD), can affect normal neuronal activity in different ways. However, In spite of intense experimental work to explain the possible underlying mechanisms of action, the impact of amyloid beta protein is poorly understood. From ion channel hypothesis, we can assume that Aβ can affect the normal activity of a neuron; for example, making a neuron more excitable (by reducing the A-or DR- type K+ currents) or less excitable (by reducing synaptic transmission and Na+current). Abnormal function of sodium channels has been proposed to contribute to hyper excitability in a manner suggesting that drugs that block sodium channels might recover the condition. The present study uses a computational model to analyze how sodium and potassium channels modulate the original firing conditions. We have first modeled the different stages of AD by progressively modifying different active channels and synaptic properties of a realistic model neuron, where all parameters are adapted from experimental findings. We then tested sodium and potassium channel manipulations that could compensate for the effects of Aβ. The ion channels are modeled using Hodgkin & Huxley formalism. The model points to possible pharmacological interventions of both sodium and potassium ion channels in term of kinetic and activation properties.

Poster Ref: P2-B-004

Theme: B: Molecular, Cellular and Synaptic Mechanisms

GABAB receptor-mediated, layer-specific excitatory and inhibitory synaptic plasticity reorganises neocortical response to stimulation.

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Repeated presentation of sensory stimuli generates transient gamma frequency (30-80 Hz) responses in neocortex that show enhancement or suppression in a task-dependent manner(1,2). Complex relationships between individual neuronal outputs and the mean, local field potential, population activity accompany these changes but little is known about the mechanism underlying this form of plasticity. Using an *in vitro* preparation of auditory cortex to allow control of cortical stimulus and neuromodulatory state we explore the lamina and synaptic basis for such plasticity in neocortex

Slices containing primary auditory cortex were prepared from adult male Wistar rats and maintained *in vitro*. Gamma-band responses were induced by two transient, focal activations of layer 4 with glutamate, delivered 1h apart. The resultant activity was recorded from all cortical layers with 10x10 Utah probes. Changes in synaptic strength were explored utilising sharp electrodes to record from individual pyramidal cells.

Repeated, transient stimulation of input layer 4 induced a highly laminar-specific change in unit recruitment and relationship between spikes and the local field potential. Unit rates and recruitment into the stimulus response were enhanced in supragranular layers and suppressed in infragranular layers despite enhanced gamma power in both layers and no net change in overall spike rates/unit recruitment through the neocortex as a whole. These differential laminar plastic changes were accompanied by contrasting synaptic plastic processes: In supragranular layers repeated stimulation induced excitatory synaptic potentiation whereas inhibitory synaptic plasticity dominated in infragranular layers. Both processes were critically dependent on activation of GABAB receptors.

These data indicate that repetitive sensory input may both enhance supragranular neuronal population responses and suppress/sharpen infragranular responses, thus optimising the cortical representation and minimising cortical output simultaneously.

This work was funded by The Welcome Trust.

1. Conrad N *et al.* (2007). Neurosci Lett. 429:126-30.
2. Gruber T *et al.* (2008). J Cogn Neurosci. 20:1043-53.

Poster Ref: P2-B-005

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Stable transfection of the prion protein gene into SH-SY5Y cells alters stress responses in a clone-specific manner.

Andrew Castle, Sonya Agarwal, Dominic Kurian, Thomas Wishart and Andrew Gill

Roslin Institute, University of Edinburgh

The cellular prion protein, PrPC, has been suggested to have various functions, including protecting cells from apoptosis and oxidative stress, maintaining mitochondrial function, regulating calcium homeostasis and modulating neuronal excitability. We are investigating the molecular mechanisms regulated by PrPC, which will increase our knowledge of its putative stress-protective functions and of how such mechanisms may be harnessed to afford long-term neuronal protection. Our work should also improve understanding of the pathogenesis of prion diseases. To investigate PrPC function, we have stably transfected the prion protein gene into SH-SY5Y neuroblastoma cells – the parental cell line lacks detectable endogenous PrPC expression. Using monoclonal lines derived from the transfected cells, we have shown that PrPC expression confers protection against the toxins paraquat, staurosporine and tunicamycin, as measured by both survival and cytotoxicity assays. Contrastingly, PrPC-transfected cells were more sensitive to serum deprivation than controls. Not all clones displayed these altered stress responses, and variability between clones cannot be explained by differences in the level or localisation of PrPC expression. Subsequent proteomic analyses are beginning to shed light on whether the differences in cellular stress responses are the result of PrPC expression or are determined by the plasmid integration site.

Poster Ref: P2-B-006

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Astrocytic IP3 receptors regulate hippocampal LTP.

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**+these authors contributed equally*

Astrocytic Ca^{2+} signaling is required for LTP at the Hippocampal Schaffer Collateral to CA1 (SC-CA1) synapse. Controversy, however, remains as IP3 receptor (IP3R) type-2 knockout mice (IP3R2KO), which are reportedly deficient in astrocytic Ca^{2+} signaling, exhibit normal LTP. It is possible that an astrocytic Ca^{2+} channel hitherto unknown is required for LTP and that some Ca^{2+} transients still prevail in IP3R2KO mice. In the current study, we address this hypothesis by visualizing sub-cellular Ca^{2+} dynamics within astrocytic processes, focusing on Ca^{2+} release through all IP3R subtypes (1,2,3) and their role in LTP.

To image Ca^{2+} dynamics in astrocytic processes we used two-photon imaging of GCaMP3 expressed in cultured hippocampal slices, and in acute slices we used the Ca^{2+} indicator Fluo-4, loaded *via* an astrocytic patch pipette. To evoke Ca^{2+} responses in astrocytes, we stimulated astrocytes with mGluR (metabotropic glutamate receptor) agonist DHPG or High Frequecny Stimulation (HFS, 1sec at 100Hz) of the Schaffer Collaterals. In contrast to the premise of previous studies, we observed substantial astrocytic Ca^{2+} responses in slices prepared from IP3R2KO mice. Since activation of mGluRs triggers Ca^{2+} release *via* the IP3Rs, we decided to investigate the contribution of other IP3R subtypes. To this end we repeated these experiments using hippocampal slices prepared from IP3R type-2/-3 double KO mice (IP3R2/3KO) and used heparin to inhibit all IP3R subtypes. With this approach we identified two new astrocytic Ca^{2+} channels, namely IP3R-1 and -3. Unlike the large global Ca^{2+} signals mediated by IP3R2, IP3R1 and 3 produce local Ca^{2+} signals confined to astrocytic processes. Inhibiting all astrocytic IP3Rs with Heparin blocked HFS induced Ca^{2+}transients in astrocytic processes.

Having identified two new functional Ca^{2+} channels in Astrocytic processes we tested their involvement in LTP. In accordance with Ca^{2+} imaging data, 2xHFS-LTP was intact in slices prepared from IP3R2KO, and IP3R2/3KO mice. Finally inhibiting all astrocytic IP3R subtypes with Heparin inhibited 2xHFS-LTP. Our results demonstrate that IP3R-1 and -3 are new astrocytic Ca^{2+} channels and that they could be required for LTP induction at hippocampal CA3-CA1 synapses.

Poster Ref: P2-B-007

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Mapping postsynaptic protein diversity in the human brain.

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The human post-synaptic proteome is highly complex consisting of over a thousand different proteins. Mutations in genes coding for these synaptic proteins have been linked to more than hundred brain disorders1 and an increasing number of psychiatric, neurological and neurodevelopmental conditions are now regarded as “Synaptopathies” or diseases of synapses. Animal studies reveal that there is heterogeneity among synapses, but little is known about the diversity of synapse types and their distribution in human brain. The human synapse is an important pharmacological target and study of these proteins with ageing and in pathological states may lead to development of new therapeutic agents. This study aims to catalogue subtypes of excitatory synapses in selected human brain regions using quantitative immunofluorescence (IF). Methods have been developed for antibody labelling and quantification of synapses expressing PSD-95/Dlg4, a membrane-associated guanylate kinase and the major postsynaptic scaffold protein implicated in a range of brain disorders.

Human control cases were selected from the Edinburgh MRC Brain Bank. Post-mortem paraffin-fixed formalin-embedded brain tissue from eleven regions commonly affected in neuropathological disorders was labelled for PSD-95. Using confocal microscopy and digital image analysis, the PSD-95 synaptic puncta fluorescence was reported as density, size and intensity per neuroanatomical area.

The PSD-95 expression showed postsynaptic puncta of different sizes and intensities. Similar patterns of expression were observed in a knock-in PSD-95 EGFP/EGFP mouse model. Diversity in the size, intensity and spatial distribution was observed within and between different human brain regions. Quantification of these parameters using G2CSynMAPP computerized analysis tools developed for the mouse brain enable systematic studies of human brain synapses composition and distribution. Future studies will aim at systematically cataloguing and quantifying synaptic protein subtypes in different brain regions. Application of these methods in diagnostic neuropathology will enable development of new quantitative methods in synaptopathies.

1. Bayes *et al.* Nature Neuroscience 2014 (1), 19-21.

Poster Ref: P2-B-008

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Behaviour dependent activity and synaptic relationships of hippocampo-subicular projecting GABAergic trilaminar cells.

Linda Katona[(1)], Damien Lapray[(1)], Ryohei Tomioka[(1,2)], Benjamin Micklem[(1)], Jozsef Somogyi[(1)], David Roberts[(1)], Kristina Wagner[(1)], Michael Crump[(1)], Abhilasha Joshi[(1)], Thomas Klausberger[(3)], Kathleen Rockland[(2)] and Peter Somogyi[(1)]

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Fast communication between temporal cortical areas is mediated by both glutamatergic and GABAergic long-range projections. In the hippocampal CA1 area, some GABAergic neurons project to the medial septum and retrohippocampal areas (1-3). Trilaminar cells are located in stratum oriens, innervate strata oriens, pyramidale and radiatum in CA1 and project to the subiculum. They strongly express muscarinic acetylcholine receptor 2 (M2+), are innervated by metabotropic glutamate receptor 8-expressing (mGluR8+) terminals of unknown origin and exhibit unique burst firing (2-4). Trilaminar cells are rarely encountered during *in vivo* recordings hence their action in behaving animals is unknown.

Here, we explored the behaviour dependent firing and the synaptic connectivity of trilaminar cells. Retrograde neuronal tracing revealed a population of subiculum-projecting trilaminar cells in CA1 located in and close to the alveus. These cells target preferentially GABAergic cells in CA1, many of which are parvalbumin-positive. The preferential targeting of interneurons was also confirmed for a trilaminar cell identified by extracellular recording and juxtacellular labelling in a freely moving rat. Extracellular recordings of putative trilaminar cells showed that behaviour segregates the action of identified trilaminar cells from other interneurons. A maximal spike frequency of >250 Hz was found during sharp wave-ripples (SWR) when an identified cell fired in bursts. Less frequently shorter bursts of spikes occurred also during the ascending phase of theta oscillations. Using anterograde labelling we show that most mGluR8+ boutons on trilaminar cells originate from GABAergic cells of the medial septum, both in the rat and in mouse, suggesting that GABA release to these interneurons is selectively suppressed when extracellular glutamate levels rise.

We suggest that the suppression of GABAergic inputs during SWR by the activation of mGluR8 allows the high frequency rhythmic discharge of trilaminar cells required for supporting the coordination of synchronous activity across regionally distributed networks.

1.Miyashita (2007) Eur. J. Neurosci., 26, 1193.
2.Ferraguti (2005) J. Neurosci., 25, 10520.
3.Jinno (2007) J. Neurosci., 27, 8790.
4.Sik (1995) J. Neurosci., 15, 6651.

Poster Ref: P2-B-009

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Protective effects of the flavonoid Quercetin against the brain damage induced by chronic unpredictable stress in rats.

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Background: Stress is known to alter the cellular homeostasis in brain and may involve various forms of neurotoxicity including neuronal death. Experimental chronic unpredictable stress (CUS) mimics the chronic stressful experiences faced by humans in daily life. The particular effects and mechanisms by which CUS induces brain damage is not fully understood. Epidemiological studies have suggested that the intake of food containing flavonoids may be associated with a reduced risk of some diseases. The particular effects of the flavonoid Quercetin (QUR) on brain damage induced by experimental chronic unpredictable stress (CUS) was not studied before.

Aim: This study aims to investigate the brain damage induced by experimental chronic unpredictable stress in rats, and to investigate the potential neuro-protective effects of Quercetin and the possible mechanisms of action implicated.

Methodology: Thirty two adult male Wistar rats were randomized to one of four groups (n=8; each): Control+vehicle, Control+ QUR, CUS+vehicle, and CUS+QUR. CUS was applied for 3 weeks, during which the vehicle (NS) or QUR (50 mg/kg) were i.p. administered daily. Oxidative, inflammatory and apoptotic parameters were measured. Data are expressed as means ±SD, and significant differences were recognised at ($P< 0.05$).

Results: In the brains of the CUS stressed rats, there was activation of the intrinsic apoptotic pathway, mediated by activation of nitrosative and oxidative stress as well as activation of proinflammatory markers in comparison to brains of the control rat. That was shown in CUS rats by significant elevations in the levels of MDA (2.3±0.04 *vs* 0.98±0.04 uM), TNF-α (2.9±0.42 vs 0.81±0.21 pg/mg), IL-6 (38.2±4.7 *vs* 18.7±2.2 pg/mg), iNOS (5.4±2.4 vs 3.1±0.48 pg/mg) and caspase 3 (0.50±0.04 *vs* 0.15±0.02 ng/mg), with concomitant decreases in the activities of SOD (10.8 ±0.76 *vs* 25.6 ±2.9 U/mg) and GPX (80.2±4.9 *vs* 121.6+8.2 nmol/min/ml) and levels of BCl-2 (2.9±0.49 *vs* 7.8±0.63 ng/mg). QUR treatment to CUS stressed brought all of these parameters to control levels.

Conclusion: This study demonstrated that supplementation with Quercetin ameliorates the brain damage induced by chronic unpredictable stress *via* its antioxidant, anti-inflammatory and anti-apoptotic potentials.

Poster Ref: P2-B-010

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Effects of resting membrane potential on the intrinsic excitability profile of adult rodent CA1 pyramidal cells.

Francesco Tamagnini[1], Talitha Kerrigan[1], Clair Booth[2], Jon Brown[1] and Andrew Randall[1,2]

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Resting membrane potential (RMP) is a key feature of neuronal physiology. In a given population of neurons RMP is not invariant – but encompasses a range of values. Furthermore, the mean RMP of a cellular population can change during development, aging, disease, and also as a result of recent electrical activity, a form of activity dependent intrinsic neuronal plasticity.

Comparison of 15 separate patch clamp studies performed in our group in recent years encompassing ~500 murine wild-type CA1 pyramidal neurons (CA1-PN) revealed the extent of inter- and intra-study variation in RMP. Correlating RMP with other neurophysiological parameters provided a first indication of how other neurophysiological properties are influenced by RMP, e.g. action potential (AP) threshold and rate of rise. To address more directly these effects of RMP we performed a study examining how within-cell changes to RMP, produced by application of appropriate bias currents, impacted upon intrinsic excitability properties of CA1-PN. In brief, the RMP of CA1-PN was set to -80, -74 and -66 mV and various current stimuli applied to either hyperpolarize or depolarize the cells. From this sub- and suprathreshold parameters were determined including AP waveform analysed for the first AP produced by a +300 pA stimulus.

During 500 ms depolarizing stimuli of various magnitudes, AP count was lower at -80 mV than either -74 or -66 mV. This difference was largely lost if analysis was restricted to sweeps in which at least 1 AP fired. Instantaneous AP frequency versus AP interval was very similar at all 3 RMPs. Input resistances were lowest at -80 mV and highest at -66 mV, as was membrane time constant; calculated capacitance was RMP-independent. Sag and rebound in response to -100 pA stimuli were greatest at -80 mV reflecting more effective HCN channel activation. As CA1-PN were depolarized to -66 mV maximum rate of AP rise decreased and AP threshold became more depolarized, both likely as a result of Na+ channel inactivation. AP width at threshold was greater in depolarized CA1-PC probably due to prior inactivation of various fast gating K+ channels. These data indicate the importance of accounting for RMP when comparing other neurophysiological features across cellular populations.

Poster Ref: P2-B-011

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Ethanol-induced G-protein subunit expression changes in D2 receptor deficient *Drosophila*.

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University of East London

Alcohol abuse and addiction impact on users' quality of life and have substantial implications for health services. Understanding the mechanisms by which alcohol modifies cellular and molecular mechanisms associated with chronic abuse, could lead to improved pharmaceutical interventions to overcome alcohol addiction. Alcohol acts through multiple receptor systems and, like other addictive drugs, causes prolonged or permanent changes in gene expression. Dopamine release and changes in gene expression of elements of the cAMP-CREB-DeltaFosB pathways have been associated to addictive behaviours. However, the mechanisms linking ethanol with long-term changes in the reward pathways are not fully understood. In this work, we have focused on measuring changes in G-protein gene expression in a Drosophila melanogaster ethanol tolerance model. Exposure of *Drosophila* to ethanol vapour causes sedation in the flies, but multiple exposure increases the sedation time, which is considered a manifestation of ethanol tolerance. Using quantitative real-time polymerase chain reaction (qRT-PCR), we have measured G-protein mRNA in flies that have experienced zero, one or three ethanol exposures at 24 hours intervals. When measured in a wild type population, changes in G-protein levels were variable. However in a sub-population of *Drosophila* that we selected for high ethanol sensitivity we observed a non-statistically significant decrease of two Gα-protein subunits: Gi and Gq. These same changes were observed at a statistically significant level in two Drosophila mutant lines characterised by a deletion of Dopamine D2 receptor and a non-functional of Gq subunit respectively. These two *Drosophila* lines also displayed an altered sensitivity to ethanol while retaining the tolerance response to alcohol. These data indicate that when measured in genetically homogeneous populations ethanol induced G-proteins gene expression changes can be detected, but the persistence of this effect in flies lacking D2 receptors suggests that these G-proteins subunits changes do not utilise the previously described D2 receptor dependant mechanisms associated with addictive drugs.

Poster Ref: P2-B-012

Theme: B: Molecular, Cellular and Synaptic Mechanisms

The role of the paranode in the formation and maintenance of nodes of Ranvier in the central nervous system.

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Myelination of axons in the central and peripheral nervous system (CNS and PNS) is required for saltatory propagation of nerve impulses at the nodes of Ranvier. The nodal regions are organized in distinct membrane domains, namely the node of Ranvier, the paranode, the juxtaparanode and the internode, and this organization promotes fast conduction. The formation and maintenance of these domains is fundamental to the efficient propagation of the electrical impulse but much remains to be learned about the underlying mechanisms.

Here we have studied the contribution of paranodal proteins and their linkage to the underlying cytoskeleton to both the formation and maintenance of CNS nodes by using a combination of knockout and transgenic rescue approaches.

We show the important role of the Caspr cytoplasmic domain, presumably through its linkage to the paranodal cytoskeleton, in clustering nodal proteins before node formation. These mice fail to form heminodal clusters of nodal components as also found in Caspr-null mice and oligodendrocyte process migration is delayed. Nevertheless, normal nodes are formed eventually in these mutants. This surprisingly results in shorter internodal lengths: in particular, we observed a significantly higher percentage of very short internodes (<250μm) in these animals compared to controls.

Further, we showed that in the mutants the paranodal structures are deranged with disruption of the nodal domain and invasion of the juxtaparanodes into the paranodal space. Surprisingly, electron microscopy showed that, in contrast to Caspr-nulls, when the C-terminus of Caspr is absent the septate axoglial junctions are still present. Nevertheless, this is not sufficient to maintain normal paranodal structure.

In conclusion, the link between the paranodal junction and the underlying axonal cytoskeleton appears to be essential both during CNS development, when myelin and nodes of Ranvier are formed, and also for the long-term maintenance of the different myelin domains.

Poster Ref: P2-B-013

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Defective synaptic vesicle recycling in a mouse model of Fragile X syndrome.

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Both autism spectrum disorder (ASD) and intellectual disability (ID) have complex aetiologies due in part to the multiple associated genetic and environmental causes. Fragile X syndrome (FXS) is a single gene disorder that causes both ASD and ID. In this syndrome, the promoter of the FMR1 gene is hypermethylated, disrupting the synthesis of fragile X mental retardation protein (FMRP). FMRP acts primarily as a protein translation regulator. In its absence, the expression levels of many proteins, including several proteins associated with the synaptic vesicle (SV) cycle, are altered. FMRP also plays other important roles in the presynapse including regulation of action potential duration in the hippocampus. Furthermore, in mouse models of the disorder (Fmr1-/y mice) the size of specific SV pools is increased.

We hypothesised that a deficit in SV recycling may be an important underlying feature of ASD and ID, particularly in the Fmr1-/y model.

To examine whether SV recycling is altered in FXS, we used the genetically encoded reporter, synaptophysin-pHluorin (sypHy) to visualise the SV cycle in hippocampal neurons from the Fmr1-/y model. SypHy allows real-time tracking of SV dynamics. Using sypHy the amount and rates of both endocytosis and exocytosis were calculated. We observed increased exocytosis only at high frequency (50 Hz) stimulation without an increased rate of retrieval in primary neuronal cultures derived from the knockout mouse hippocampus as compared to wildtype littermate controls. We also used western blotting to assess expression of proteins involved in the synaptic cycle and identified some potential protein targets with increased expression levels that may underlie the increased exocytosis that we observed.

Poster Ref: P2-B-014

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Sphingosine 1-Phosphate Receptor-1 (S1P1R) distribution in the young and aged rat brain.

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Sphingosine 1-phosphate (S1P) is a bioactive lipid generated from sphingosine through the action of sphingosine kinases (SphK1 and SphK2). S1P regulates many important cellular functions such as angiogenesis, neural development, cell migration, cell survival and lymphocyte chemotaxis. It achieves these pleiotropic effects through activation of a family of five G protein-coupled receptors (GPCRs) named S1P1R to S1P5R. S1P receptors show cell type-specific expression patterns which underpin its wide-ranging functions in the cardiovascular, immune, and central nervous systems (CNS). This study focuses on the S1P receptor subtype-1 (S1P1R). Here, we investigate how S1P1R expression changes in the rat brain from youth to adulthood. S1P1R is involved in various key CNS functions during development, including vascular maturity and microglial migration. The S1P1R is coupled to the Gi/o alpha subunit and thus inhibits adenylyl cyclase and reduces cAMP production in cells. Activation of S1P1R also results in a rise in intracellular calcium levels which can activate many downstream signalling cascades leading to cytoskeletal rearrangements. Using immunofluorescence and image analysis techniques, we analysed S1P1R expression and regional localisation in P9, P37 and P450 day old rat brains. At 9 days old, S1P1R is highly expressed in most cortical layers with lower levels in the auditory cortex. It is also highly expressed in the non-neuronal cell layers of the hippocampus and cerebellum. At 37 days old, S1P1R expression appears to decrease in the cortex and increase in the hippocampus. This pattern of expression is generally maintained in 450 day old rat brains with the highest expression measured in the CA1 stratum radiatum and CA1 stratum oriens regions of the hippocampus. S1P1R is also highly expressed in the granular and molecular layers of the cerebellum at 450 days old. S1P1R expression appears predominantly non-neuronal as it does not co-localise with neurofilament H staining. The redistribution of the S1P1R in the rat brain from neonatal developmental stages through to adulthood may represent key changes in its role in CNS functioning. Future work will focus on determining the role of S1P1R in the hippocampal CA1 region of aged rats.

Poster Ref: P2-B-015

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Conservation and divergence of the activity-dependent transcriptome of mouse and human neurons.

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Many neuronal processes including development, survival and plasticity, rely on activity-dependent changes to the transcriptome. Whilst much has been learnt from studies of rodent neurons, the degree of conservation between rodent and human neurons is unknown. Using RNA-seq, we compared the activity-dependent transcriptome of mouse cortical and cortical-patterned human ES cell-derived neurons in response to L-type Ca^{2+} channel activation. This revealed considerable overlap in the activity-responsiveness across species. However, a substantial number of genes were uniquely regulated in either mouse or human neurons. Species-specific gene induction was confirmed using mouse cortical neurons from Tc1 mice, which carry human chromosome-21, allowing for direct comparison of mouse and human gene expression from the same neurons. Analysis of the promoter regions of uniquely regulated genes in both mouse and human neurons revealed differences in transcription factor binding sites that could underlie species-specific gene induction. Mutation of the differential transcription factor binding sites confirmed their role in species-specific gene induction. The level of conservation in the activity-dependent transcriptome across species suggests that rodent neurons are good model for studying activity-dependent early gene expression, however, the divergences identified in this study may impact on how these neurons functionally interpret electrical activity.

Poster Ref: P2-B-016

Theme: B: Molecular, Cellular and Synaptic Mechanisms

PTEN deletion combined with alpha9 integrin expression enhances adult corticospinal tract regeneration.

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Central nervous system (CNS) axons do not regenerate after injury although several experimental treatments have shown promise for nervous system repair. Although, the extracellular matrix glycoprotein, tenascin-C, is highly expressed after CNS injury, lack of its receptor in the adult CNS (alpha9 integrin) contributes to strong inhibition of growth through the lesion site. To counteract this, we have previously demonstrated that reintroduction of the alpha9 integrin receptor promotes axonal regeneration after dorsal rhizotomy or dorsal column crush lesion to modest levels *in vivo*. Further ongoing studies have suggested that following exogenous expression of integrins within the CNS using gene therapy vectors, there is a defect in axonal localisation and transport of these integrins within the adult corticospinal tract (CST). This defect is not present in systems with a greater propensity for regeneration such as in the neonatal corticospinal tract, or in the peripheral nerve. From another perspective on CNS repair, studies evaluating the effects of either conditional deletion or suppression of the phosphatase and tensin homolog (Pten) gene have demonstrated significant levels of axonal regeneration in the corticospinal tract and optic nerve. These studies showed an upregulation of mTOR (mammalian target of rapamycin) as a result of Pten deletion, generating an increased regenerative ability within the CNS. By enhancing neuroprotection and an intrinsic regenerative capacity by Pten deletion while promoting axonal growth with alpha9 integrin expression, we therefore hypothesize these two therapies combined will promote significant levels of axon regeneration in the adult CST further than either alone. These studies were performed by conditional deletion of Pten in corticospinal neurons at birth, followed by injection of AAV-alpha9integrin-V5 injected into corticospinal neurons at 8 weeks concurrent with a T8 spinal cord crush lesion. CST axons were anterogradely traced with biotinylated dextran amine to anatomically examine long-term regeneration at 8 weeks post-injury. Our preliminary results suggest a strong combinatorial effect on CST axon regrowth following Pten deletion and overexpression of alpha9 integrin in corticospinal neurons.

Poster Ref: P2-B-017

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Generation of multiinnervated dendritic spines and memory formation in ageing.

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Hippocampus-dependent memory formation in old age depends on modification of neural circuits and in particular the generation of multi-innervated dendritic spines (MIS, see Fig.1). MIS generation is the mechanism of memory formation when strengthening of existing synapses is impaired (Radwanska *et al.*, 2011). It slows down memory formation in older animals and impairs flexibility of newly acquired memory compared to young animals. We have analysed MIS generation in the hippocampus before and after contextual fear conditioning (FC) in following wild-type groups of mice

• young adult (n=3, 18 weeks): (i) naïve and (ii) 24 hours after FC;
• aged mice (n=3, 18 months): (i) naïve,(ii) 2 hours and (iii) 24 hours after FC.

Mice were perfused intracardially and brain slices were used for electron microscopy, 3-D reconstructions from serial ultrathin sections were performed to allow quantitative analyses of structural changes in dendritic spines and post-synaptic densities in hippocampal CA1 stratum radiatum. As the number of MIS in the brain tissue is very small, we developed a method of serial section imaging in transmission electron microscope (TEM) by acquiring montages and correcting chromatic aberrations of single frames due to uneven electron beam. This procedure makes stitched montages easier to align to each other and provides a larger volume of tissue for analysis of synapses (single frame vs 3x3 montage: ~500 vs. ~2000 synapses respectively).

Synapse density analysis showed a significantly increased number of synapses in the group 24h after FC in young animals comparing to young naïve. Moreover, all groups of aged animals had a higher synapse density compared to young naïve, although only the FC24h aged group showed significant difference (subject of increase number of animals per group to make bigger statistics).

Analysis showed a significant increase of MIS number in all groups of aged animals compared to young naïve. Interestingly the young FC24h group had an increased number of MIS but this was not significantly different.

Therefore we conclude that MIS have important role in aging.

Supported by BBSRC Grant.

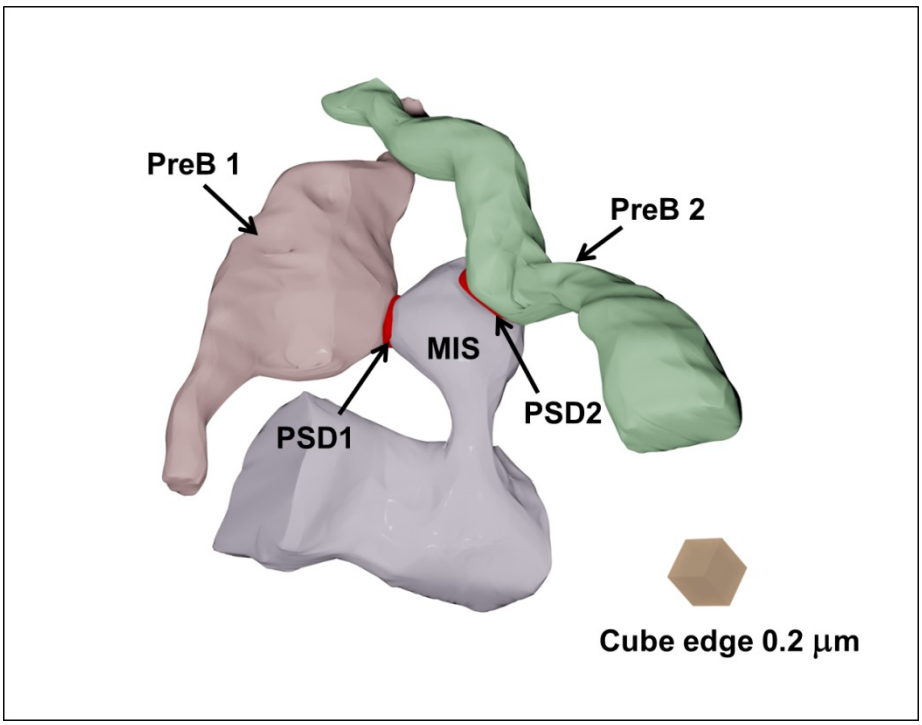

Fig. 1 Three-dimensional reconstruction from serial EM sections of multi-innervated spine (MIS). PreB, presynaptic bouton; PSD, postsynaptic density.

Poster Ref: P2-B-018

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Modulation of sphingosine 1-phosphate (S1P)-induced calcium responses in Abeta42-treated mouse glial cells.

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Alzheimer's disease (AD) is thought to progress, in part, due to toxic amyloid beta (Abeta42) protein accumulation in affected brain regions, leading to neurodegeneration. Abeta42 also affects astrocyte functioning in the brain and can alter calcium homeostasis. It has recently been reported that levels of the neuroprotective lipid signalling molecule, sphingosine 1-phosphate (S1P), are reduced early in AD pathology. Abeta42 may, therefore, affect S1P production and/or metabolism in amyloid plaque-loaded brain regions. Astrocytes express high levels of certain S1P receptor subtypes, particularly S1P1R. The drug FTY720 (fingolimod) acts as a functional antagonist at the S1P1R causing rapid and sustained internalisation and persistent signalling within the cell. FTY720 can also inhibit the release of pro-inflammatory mediators from astrocytes under certain conditions. The aim of this study was to investigate the effects of Abeta42 treatment on cultured mouse astrocytes. Specifically, S1P-mediated calcium responses in astrocytes were assessed following 24 h pre-treatment with Abeta42. Astrocytes were also co-treated with the S1P receptor modulator, FTY720, in order to assess its influence on Abeta42-induced alterations in S1P-mediated calcium influx. Cultured astrocytes were loaded with fluo-4AM calcium indicator and prepared for live-cell calcium imaging experiments. Time-lapse fluorescence images were captured at a frame rate of 1 Hz and changes in calcium fluorescence intensity were measured in each cell using automated image analysis techniques. Abeta42 pre-treatment attenuated S1P-mediated calcium influx in mouse astrocytes. This reduction of calcium influx was slightly attenuated by co-application with FTY720. Pre-treatment with FTY720 alone, however, caused a sustained increase in intracellular calcium in astrocytes in response to S1P application. Taken together, these results highlight the chronic effects of Abeta42 treatment on S1P-mediated calcium influx in astrocytes and a possible role for FTY720 in attenuating this effect. Future work will focus on the effects of Abeta42 treatment on S1P1R expression in astrocytes and the mechanism whereby Abeta42 affects S1P-mediated calcium responses.

Poster Ref: P2-B-019

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Investigating BDNF dependent morphological changes in hippocampal neurons.

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Neurons extend axons and dendrites to cover large areas, and accordingly synaptic connections at distal axonal processes are far from the cell soma. A key question in neuronal biology is: how is information transmitted from the distal axonal to the soma, the site of gene regulation? How this information is subsequently integrated and interpreted at the soma to modulate neuronal function may inform our understanding of neuronal network development, refinement and plastic modulation.

Neuronal plasticity is closely coupled to activity-dependent events in order to strengthen active synapses and abolish or dampen unused connections. The neurotrophin brain-derived neurotrophic factor (BDNF) provides an example of an activity regulated molecule able to trigger intracellular processes which modulate neuronal plasticity. BDNF signals through the membrane tyrosine kinase receptor TrkB. TrkB activation by BDNF has been shown to enhance neuronal growth, arborisation, axonal branching and synaptic transmission. However, the precise intracellular mechanisms underlying the effects of BDNF on plasticity are not well characterised. Specifically what are the local and long-range axonal signaling pathways activated by TrkB-BDNF, and what is their outcome on cellular function?

We are using microfluidic devices to isolate distal axons and systematically identify signals, which are initiated by BDNF at distal sites and are trafficked to the somatodendritic compartment. Using this approach, we have shown that distal stimulation retrogradely activates somatic ERK signaling and can initiate IEG expression and in the somatodendritic compartment.

Furthermore, we are adapting the microfluidic devices to allow spatial-temporal control of BDNF application to the distal axonal compartment. Such controlled application may allow us to tease out signaling paradigms which are activated *in situ* and not observed during bulk flow application. Additionally, we will exploit the compartmentalisation of the neuronal sub-compartments for live imaging analysis to allow tracking of morphological changes in the neurons after distal BDNF application.

Poster Ref: P2-B-020

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Molecular determinants of Neto1, Neto2 and GluK2 kainate receptor protein trafficking.

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Auxiliary subunits of ionotropic glutamate receptors are defined as proteins which have a regulatory function over their interacting partners, affecting the biophysical properties of receptors, and in some cases, cellular trafficking. Of these auxiliary proteins, recent studies have identified the transmembrane neuropillin and tolloid like proteins Neto1 and Neto2 as kainate receptor (KAR) auxiliary subunits, altering the functional characteristics of these receptors and possibly providing more diversity to KAR function within the CNS. However, the trafficking and expression of Neto proteins and how they regulate KARs is not well understood. Therefore, through the use of mutated Neto protein variants and utilising various molecular biology techniques including surface biotinylation, co-immunoprecipitation and EndoH/PGNaseF degradation assay, the aim of this study was to determine the mechanisms involved in the trafficking of Netos from the ER and their expression at the plasma membrane. Firstly, mutation of putative glycosylation sites on Netos showed that both Neto1 and Neto2 contain one N-glycosylation site and that the glycosylation of this site is required for both the surface expression and stability of the protein. Moreover, trafficking of Neto2 from the ER is dependent on the interaction of the GluK2 subunit whereas Neto1 was expressed at the surface independently of KAR pore-forming subunit interactions. At the plasma membrane, Neto1 was stably expressed with significantly less internalisation in basal and activated (10μM kainate treatment) states compared to Neto2. Furthermore, this difference in Neto surface expression was found to have an effect on the rate of internalisation of GluK2 KAR subunit, with GluK2 endocytosis reduced when expressed with Neto2 but not Neto1. Collectively, this data improves our understanding of how Netos contribute to the complexity of glutamate receptor regulation and function within the CNS.

This work was supported by the Biotechnology and Biological Sciences Research Council, UK (grant BB/J015938/1).

Poster Ref: P2-B-021

Theme: B: Molecular, Cellular and Synaptic Mechanisms

The role of endothelin signalling during myelination.

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Myelination, the process of axonal wrapping by oligodendrocytes, is a tightly regulated programme. Endothelin-1 and endothelin-2 have recently been shown to incur conflicting outcomes on myelination both acting *via* endothelin receptor B (EDNRB). Here we resolve this conflict through the manipulation of EDNRB signalling in rat oligodendrocytes on synthetic microfibers resulting in regulation of myelin sheath number with no effect on sheath length. Additionally EDNRB mutant zebrafish have more oligodendrocytes yet individual cells produce fewer myelin sheaths. From these results we propose a model whereby EDNRB regulates different stages of myelination through opposing distinct mechanisms.

Poster Ref: P2-B-022

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Gliotransmitter release mechanisms in rodent somatosensory cortex.

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The release of gliotransmitters (GTs) from astrocytes modulates synaptic and neuronal network activity, and so is of great importance in the normal and pathological brain. Various mechanisms of GT release have been proposed, such as *via* calcium dependent vesicular release, glutamate transporters, large pore channels, ion channels such as TREK1 and Bestrophin-1 (Best-1), and hemichannels. We have previously shown that GT release can undergo plasticity resulting in enhanced spontaneous release (Pirttimaki *et al.* 2011). In this study we investigated the mechanism underlying NMDA receptor mediated slow inward current (SIC) generation in an enhanced release model. Patch clamp recordings were conducted in layer 2/3 pyramidal neurons in rat thalamocortical slices from animals at P10-P28. TTX-insensitive SICs (defined as having an amplitude >20pA and rise time >20ms) were observed at an average of 7.46 ± 1.33 SICs/minute at 33°C. SICs were not abolished by inhibition of anion channels such as Best-1 by DIDS 200μM, TREK1 by fluoxetine 100μM, or VGLUT by Rose Bengal 0.5μM. SICs still occurred in zero calcium and EGTA containing extracellular medium, suggesting that SICs are independent of extracellular calcium, neither were they blocked in the presence of Ca^{2+} ATP-ase inhibitor CPA 10μM. Similarly, there was no significant difference in SIC rate between wild-type and inositol 1,4,5-triphosphate (IP3) type-2 receptor knock-out mice, indicating that spontaneous SIC emergence can be independent of IP3 mediated intracellular store calcium release. Together, these results suggest that this enhanced astrocyte EAA release model is resistant to pharmacological blockade of individual efflux pathways.

Pirttimaki TM, Hall SD, Parri HR (2011) Sustained Neuronal Activity Generated by Glial Plasticity. Journal of Neuroscience 31:7637-7647.

Poster Ref: P2-B-023

Theme: B: Molecular, Cellular and Synaptic Mechanisms

A Zebrafish (Danio Rerio) model of gba1 deficiency and tau over-expression.

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Objective: To determine if Tau over expression leads to dopaminergic neuronal loss in a zebrafish model of gba1 deficiency

Background: Parkinson's disease (PD) is characterised by the loss of dopaminergic neurons within the substantia nigra (SN). The pathological hallmark is the presence of Lewy bodies. Mutations in the glucocerebrosidase encoding gene (GBA1) and distinct haplotypes of the microtubule associated protein tau gene (MAPT) have been identified as genetic risk factors for PD. Homozygous GBA1 mutants develop Gaucher's disease (GD), the most common inborn error of metabolism. Adults with GD have a higher risk of developing PD. Both GBA1 deficiency and accumulation of the substrate glucosylceramide have been observed in Lewy bodies and in the SN *in vivo*. Zebrafish (*Danio rerio*) are emerging as a new vertebrate model to study neurodegenerative diseases.

Methods: A stable line of gba1+/- loss of function mutant zebrafish was out-crossed with a previously published transgenic zebrafish line over-expressing tau (Paquet *et al.* 2009). Embryos were sorted for transgenicity and raised to adulthood. Adults were genotyped to identify gba1+/- expressing transgenic tau, and in-crossed to generate embryos which were sorted from 24hpf and fixed at 5dpf in 4% paraformaldehyde. Whole mount in-situ hybridisation was performed using a tyrosine hydroxylase (TH) probe. Embryos were bisected and tail tissue used to genotype for gba1 by PCR. TH positive neurons were counted in 10 embryos of each genotype under 20x microscopy in the dopaminergic subgroups identified by Rink and Wulliman (2002). This was carried out in triplicate (n=3) and TH counts were normalised to non-transgenic wild type siblings. The number of dopaminergic neurons in transgenic tau embryos of all gba1 genotypes was compared to non-transgenic counterparts using ordinary one-way ANOVA statistical analysis.

Results: No significant difference between mean normalised dopaminergic neuron counts of all 6 genotypes was detected.

Conclusion: Both *in vitro* and *in vivo* data suggest that alpha-synuclein protein levels and mediated neurotoxicity may be increased by GBA1 deficiency. Our data suggest that this is not the case for Tau. We are currently studying the effect of GBA1 deficiency in juvenile and adult zebrafish.

Poster Ref: P2-B-024

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Synchonous neuronal responses evoked by astrocytic glutamate release.

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Gliotransmission is increasingly being recognised as a vital component of brain function. Astrocytic release of neurotransmitters such as glutamate, GABA, ATP and adenosine has been demonstrated to alter the properties of neuronal activity and play a role in diverse functions such as basic modulation of synaptic activity (such as the “tripartite synapse” model) and long-term plasticity. Furthermore, the extensive processes of astrocytes are capable of reaching up to 100,000 synapses across many neurones. One form of astrocytic neurotransmitter release generates slow inward currents (SICs) in neurones, recognisable by their slow rise and decay times, largely through activation of extrasynaptic NMDA receptors by glutamate. Although SIC generation is independent of TTX and largely independent of synaptic activity, sustained stimulation of afferents have been observed to cause long-term enhancement (LTE) of SIC rates in ventro-basal thalamic (VB) neurones. In this study, using an enhanced astrocytic release model, we have investigated *in vitro* synchronous SIC generation in multiple neurones in VB, barrel cortex and CA1 hippocampus of rat brain slices.

SICs were observed in the form of spontaneous Ca^{2+} responses (SCRs) in neurones loaded with Fluo-4 in the presence of TTX and 0 Mg^{2+}. Enhanced release conditions greatly increased the frequency of SCRs over control, from 1.1 ± 0.3 min-1 to 9.3 ± 1.5 min-1 (VB), 2.0 ± 0.5 min-1 to 10.3 ± 2.4 min-1 (cortex)and 0.9 ± 0.3 min-1 to 13.4 ± 3.4 min-1 (CA1). SCRs were almost abolished in the presence of D-AP5, confirming their dependence on NMDA receptor activation. Synchronicity was measured by three or more neurones having SCRs occurring within 2 seconds. It was found that in the enhanced release model, 42 ± 8% of SCRs in the VB, 48 ± 19% in cortex, and 39 ± 10% in CA1 were synchronous. These were all significantly greater than a computer-generated random release model with similar SCR rates. We conclude that astrocytic glutamate release is capable of generating SICs in multiple neurones, and these are strong enough to cause intracellular Ca^{2+} elevations. This has important implications for astrocytic ability to co-ordinate activity across multiple cells, particularly with regard to LTE.

Poster Ref: P2-B-025

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Synaptic vesicle release regulates the growth of myelin sheaths along single axons *in vivo*.

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In recent years, increasing evidence suggests that neuronal activity dependent regulation of central nervous system myelination might be an important form of nervous system plasticity. However, the effects of neuronal activity on myelin sheath growth have not been demonstrated *in vivo*. Here, we use zebrafish to identify individual CNS axonal subtypes that are myelinated and to characterise myelin sheath growth over time at sub-cellular resolution. We find that distinct myelin sheaths made by the same oligodendrocyte can have very different lengths and also grow at very different rates, suggesting local axonal control of myelin sheath growth. We also find that myelin sheath length along the axons of distinct neuronal subtypes is very stereotyped at any one time, further suggesting local control of myelin sheath growth. To functionally investigate the hypothesis that the activity of single axons can affect their myelination, we disrupted synaptic vesicle release along the length of individual axons in an otherwise normal environment and observed the effects on myelination. We find that the number of myelin sheaths along single axons is dependent on the activity of some subsets of axons, but not others, but that the length of myelin sheaths is reduced along all axons. Interestingly, we find that initially shorter myelin sheaths can catch up in length with normal myelin sheaths over time, suggesting that activity is not required for myelin sheath growth *per se*, but that it regulates the speed of myelin sheath growth. These data have important general implications for activity dependent myelination and nervous system plasticity.

Poster Ref: P2-B-026

Theme: B: Molecular, Cellular and Synaptic Mechanisms

The roles of voltage-gated calcium channels (VGCCs) in the control of striatal dopamine release are variable and dynamically regulated.

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University of Oxford

Voltage-gated calcium channels (VGCCs) operate differently in dopamine (DA) neurons of SNc compared to VTA, neurons which are respectively sensitive and resistant to degeneration in Parkinson's disease. There is still much to understand about the VGCCs on the vast striatal axonal arbors of DA neurons that control striatal DA release. Previous studies will have been confounded by the VCGGs that operate on cholinergic interneurons and regulate ACh release, which in turn modulates and drive DA release. We have investigated which VGCC subtypes on DA axons operate in dorsal and ventral striatum to control DA release.

We used fast-scan cyclic voltammetry (FCV) at carbon-fibre microelectrodes in mouse acute striatal slices to determine the roles of VGCCs subtypes in striatal DA release using specific blockers of N, P/Q, L, and T-type channels (ω-Conotoxin GVIA, 100 nM; ω-Agatoxin IVA, 200 nM; Isradipine, 5 μM; and NNC 55-0396, 1 μM respectively), in the presence of the nicotinic receptor antagonist DHßE (1 μM) to remove the confounding effects of ACh on DA terminals. We determined that at 2.4 mM extracellular Ca^{2+}, N>P/Q>T and L-type channels control DA release in dorsal striatum whereas only N>P/Q-type channels contribute in ventral striatum. However, "silent" L- and T-type channels in ventral striatum had a role unmasked by increasing extracellular Ca^{2+}. We also reveal that DA release in response to tonic versus phasic patterns of activity is a general function of calcium availability and not in fact dependent on specific VGCC subtypes operating at specific frequencies. Furthermore, data suggest that auxiliary α2δ subunits also modulate the VGCCs that control DA release. In summary the VGCCs that control striatal release are of many types, and are dynamically involved according to striatal region, Ca^{2+} concentration, auxiliary subunits and stimulation frequency.

Poster Ref: P2-B-027

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Evidence against a role for the novel cannabinoid receptor GPR55 in regulating cerebellar granule cell neurite outgrowth and viability.

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GPR55 is a novel lipid-sensing orphan G-protein coupled receptor (GPCR) that is activated by the endogenous lipid, L-α-lysophosphatidylinositol (LPI) and a subset of cannabinoid ligands. Interestingly, the diaryl-pyrazole antagonists/inverse agonists of cannabinoid receptor-1 (CB1), AM251 and the structurally related compound SR141716A (Rimonabant), have been shown to induce agonistic effects at GPR55. GPR55 mRNA is expressed widely throughout the body, including high levels in the brain. Previous work has indicated a role for GPR55 in LPI-induced neurite retraction in PC12 cells (Obara *et al.* 2011), a model neuronal cell line. However, effects in primary neurons remain to be established.

Given that GPR55 is expressed in the cerebellum (Wu *et al.* 2013), the aim of the present study was to utilise molecular imaging techniques to evaluate the role of GPR55 in regulating neurite outgrowth and viability in cultured cerebellar granule cells (CGCs). Propidium Iodide staining was used to identify dying cells. We found that overnight treatment with AM251 or SR141716A both induced neurite retraction and exhibited toxicity at concentrations of 3-10 μM. However, toxic effects were not blocked by the novel, selective GPR55 antagonist C390-0219 (CID16020046) at 3-10 μM. Treatment with LPI itself (10 μM) was without effect. C390-0219 was capable of inhibiting LPI-induced Ca^{2+} mobilisation (3 μM C390-0219 + 1 μM LPI = 0.059 ± 0.013 ratio units, 75.8 ± 0% inhibition) and pCREB activation (10 μM C390-0219 + 1 μM LPI = 0.262 ± 0.017 units, 62.4 ± 0% inhibition) in a HEK293 cell line stably expressing human GPR55. LPI responses in cells expressing recombinant mouse GPR55 were also inhibited. These data suggest that AM251 and SR141716A do not mediate their neurotoxic and morphogenic effects *via* GPR55 in CGCs and that GPR55 does not regulate morphological changes in these cells. These findings emphasise the importance of selective pharmacological tools for GPR55 in order to validate the physiological and pathological functions of this orphan GPCR.

References:

Obara *et al.* (2011) Lysophosphatidylinositol causes neurite retraction *via* GPR55, G13 and RhoA in PC12 cells. PloS One.

Wu *et al.* (2013) GPR55, a G-protein coupled receptor for lysophosphatidylinositol, plays a role in motor coordination. PloS One.

Poster Ref: P2-B-028

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Muscarinic acetylcholine receptors regulate the synaptic activity of neurons of the cerebellar nuclei.

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It is unclear how the cerebellum carries out any particular function, even for its well-established involvement in motor control. While many studies have focussed on the properties of inputs to Purkinje cells (PCs) of the cerebellar cortex, little is known about how PCs communicate information to their target neurons in the cerebellar nuclei (CN). The CN are responsible for extra-cerebellar projections, so studying their synaptic inputs will enhance our understanding of cerebellar outputs.

In this study visualised whole-cell patch clamp recordings were performed on CN neurons in juvenile rat cerebellar slices. Electrical stimulation of the white matter surrounding the CN was used to elicit a postsynaptic response. Inhibitory GABAergic inputs from PCs to CN were examined during pharmacological blockade of excitatory transmission. Excitatory glutamatergic inputs from mossy fibres and climbing fibres were examined during pharmacological blockade of GABAergic transmission.

Bath application of the cholinergic receptor agonist carbachol (10μM) produced long-term depression (LTD; 29.4±11.9%) of the inhibitory postsynaptic currents evoked by electrical stimulation of PC axons. This effect was inhibited by the muscarinic receptor antagonist scopolamine (10μM). Carbachol also produced LTD (41.9±11.9%) of excitatory postsynaptic currents resulting from the stimulation of mossy fibre and climbing fibre axons. Similarly, this LTD was inhibited by scopolamine. Under whole-cell current clamp recording conditions spontaneously firing CN neurons underwent depolarisation of the membrane potential (6.04±1.17 mV) and on average doubled the action potential frequency in response to carbachol; both of these effects were prevented during co-application of scopolamine.

It has been shown previously in anatomical studies that cholinergic fibres project to both the cerebellar cortex and CN (Jaarsma *et al.* 1997). Here we provide evidence of a functional cholinergic influence on the CN which appears to be mediated by muscarinic acetylcholine receptors. Further experiments will investigate the consequence of physiological stimulation of cholinergic inputs to CN and *in vivo* techniques will also be used to probe behaviours potentially mediated by the cholinergic system in the cerebellum.

Poster Ref: P2-B-029

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Characterizing the unique protein complexes formed by PSD95 and SAP102 in the post-synaptic density of the brain by IP-LC-MS/MS.

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Introduction: The membrane-associated guanylate kinases (MAGUKs), also known as the Discs Large homolog (Dlg) family of postsynaptic scaffold proteins, directly bind NMDARs and interact with numerous other proteins to orchestrate the formation of signalling complexes found in the postsynaptic terminals of brain synapses. Both the mouse and human genome encode four Dlg family members: Dlg1 (SAP97/hDlg), Dlg2 (PSD93/ Chapsyn110), Dlg3 (SAP102) and Dlg4 (PSD95/SAP90). Mutations in the genes encoding the Dlg family of synaptic scaffolding proteins as well as their interacting partners and the NMDAR subunits themselves cause various diseases with a broad spectrum of psychiatric, cognitive and motor phenotypes. We have used various proteomics methods to characterise Sap102 synaptic signalling complexes in the PSD in order to uncover how the deletion of this Dlg family member results in mental retardation and the perturbation of signalling pathways critical to cognition in the brain.

Methods: Transgenic mice expressing eGFP-PSD95 and mKO2-Sap102 were generated in our laboratory. PSD proteins were isolated from transgenic mice expressing GFP-PSD95 and mKO2-Sap102. These proteins were analysed by BNP western blotting, 2D BN-to SDS-PAGE western blotting, IP-western, IP-LC-MS/MS and label-free quantitation and profiling by mass spectrometry.

Results and Discussion: IP-LC-MS/MS data indicate that Sap102 and PSD95 interact with entirely unique sets of proteins in the brain. BN-PAGE to SDS-PAGE results clearly demonstrate that PSD95 protein complexes are between ~2.0 MDa – 0.8 MDa, while Sap102 complexes are between 0.8 MDa - 0.3 MDa and NMDARs are most abundant in the ~2.0 MDa – 0.8 MDa complexes.

Conclusions: For the first time, we have shown that PSD95 and Sap102 form unique protein complexes in the adult brain. These complexes are very distinct in their molecular weight distribution and their composition. Our results clearly indicate that these two key post-synaptic signalling molecules govern cognition through unique pathways.

Poster Ref: P2-B-030

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Paxillin associates with endocytic machinery in favor neurite sprouting.

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Neurite sprouting is the first step of neuronal morphogenesis governed by genetic and environmental factors. We utilized neuron-enrichment, elasticity-tunable substrates to investigate cooperative balance between membrane dynamics and focal adhesions in newborn neurons. We found hippocampal neurons changed their relative abundance in a subset of endocytic and focal adhesion proteins by mechanically induced co-stabilizing Cdc42 interacting protein 4 (CIP4) with paxillin. In brain or on neuritogenesis permissive substrates (< 1 kPa), elevated CIP4 expression competed against vinculin for binding to paxillin, which in turn recruited paxillin into endocytic machinery. BDNF application or cAMP elevation triggered robust endocytosis and restored the defective neurite outgrowth on non-permissive environment (20 kPa). In addition, knocking down the expression of paxillin by shRNA caused reduced endocytosis and delayed neurite sprouting in developing cortical neurons. Such defective phenotype can be rescued by CIP4 overexpression. Thus, a switch of paxillin from focal adhesion complex to endocytic machinery modulates membrane dynamics in favour of neurite sprouting.

Poster Ref: P2-B-031

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Molecular mechanisms underlying rapid estrogenic-modulation of cortical connectivity.

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There is increasing evidence that the regulation of structure and function of neuronal circuits is an essential component of normal cognitive function and behaviour. Several studies have demonstrated concurrent changes in connectivity between neurons during and following the acquisition of learned behaviours. Estrogens have repeatedly illustrated to have powerful influences over cognitive function and behaviour, which is believed to be, in part, driven by estrogenic-regulation of neuronal connectivity. It is becoming clear that estrogens have two modes of actions: classic mode of action, which takes hours to days to manifest relying on gene transcription and a rapid manner, with effects occurring within minutes to hours. These rapid effects can result in the initiation of signalling pathways leading to a number of cellular events, many of which are independent of gene transcription, *e.g.* local protein translation. Moreover, it is becoming clear that estrogens can also rapidly regulate specific behaviours. However, the molecular and cellular mechanisms that underlie this rapid regulation of behaviour have yet to be fully elucidated.

As the remodelling of cortical connectivity is believed to be an essential component of cognitive function, we have focused on understanding how estrogens can regulate dendritic spines, the site for the majority of excitatory synapses, on cortical neurons. We are currently investigating the signalling pathways that are initiated by acute estrogenic treatment, and are interested in how these pathways drive estrogen-dependent spine formation. In addition, we are interested in understanding which estrogen receptor(s) mediate the rapid (acute) actions of estrogens to the remodelling of dendritic spines on cortical neurons, and also the role of specific kinases underlying this estrogen-mediated synaptogenesis and local protein translation. By further elucidating the molecular underpinnings of rapid estrogenic-modulation of cortical connectivity, we hope to add to the growing understanding of how estrogens rapidly regulate behaviour.

Poster Ref: P2-B-032

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Subunit composition of synaptic and extra-synaptic NMDARs at juvenile synapse.

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It has been suggested that a switch in NMDAR subunit composition occurs early during postnatal development from predominantly GluN2B subunit containing receptors to GluN2A containing NMDARs in adults. Furthermore, GluN2B subunits are thought to be preferentially restricted to extrasynaptic sites and little is yet known about the expression of GluN2D subunits.

We investigated synaptic and extrasynaptic NMDARs at the Schaffer collateral (SCCP)-CA1 synapse in acute hippocampal slices from p7-8 Wistar rats maintained at 28°C. In whole cell experiments we recorded pharmacologically isolated NMDAR-EPSCs whereas activation of extrasynaptic NMDARs was achieved using TBOA. NMDAR subunit composition was probed using GluN2A (NVP-AAM077, NVP), 2B (Ro 25-6981, Ro) and 2D (UBP 145, UBP) subunit preferring antagonists.

Investigation of synaptic currents revealed that application of NVP (100 nM) blocked synaptic NMDAR-EPSCs by 44.8 % (± 12.2 %). In 1/4 cases NMDAR-EPSCs became slower after NVP, however in the 3 other cases the decay time was not affected. Subsequent application of Ro (1 µM) blocked the residual current by 76.1 % (± 3.0 %) resulting in 87.1 % (± 4.0 %) inhibition. Application of 1 µM Ro alone decreased the EPSC amplitude by 55.4 % (± 5.9 %, n=10), i.e. Ro was less potent alone than after NVP application (55 % vs. 76 %). The residual current after application of 1 µM Ro was sensitive to 10 µM Ro and decreased EPSCs by 89.4 % (± 1.7 %) of the initial current. In 5/12 cases Ro did not affect the EPSC decay time. However, in 4 experiments we observed an acceleration of the early EPSC decay phase. UBP 145 (10 µM) blocked 68.3 % (± 7.5 %) of the current and did not change the decay time of EPSCs in 4/4 experiments.

Extrasynaptic NMDAR currents were potently reduced by 1 µM Ro, which prolonged their decay time. EPSC decay profiles were not affected by subsequent application of NVP or UBP.

In conclusion, our data suggests that the synaptic NMDAR population in p7-8 rats is constituted of tri-heteromeric GluN1/GluN2A/GluN2B and di-heteromeric GluN1/GluN2B receptors, whereas extrasynaptic NMDARs are largely GluN1/GluN2B di-heteromers. Moreover, juvenile rats do not seem to express functional GluN2D containing NMDARs at the SCCP-CA1 synapse.

Poster Ref: P2-B-033

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Region-dependent diversity of the microglial transcriptome in the healthy adult brain and impact of ageing.

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Microglia are established as key immune effector cells in the CNS. Increasing evidence supports and expands our knowledge regarding microglial homeostatic functions during brain development and adult steady-state. Heterogeneity in structure, cytoarchitecture and function across the CNS would be expected to place diverse demands on microglia. A better knowledge of microglial heterogeneity and their capacity for adaptation to distinct environmental conditions is needed to understand how microglia support normal brain function and may reveal region-specific sensitivities predisposing to age-related neurodegeneration. Here we show region-dependent microglial diversity on a genome-wide scale and functional pathways underlying adult steady-state microglial diversity as well as the impact of ageing on regionally distinct transcriptional profiles.

Adult mouse microglia were purified from discrete brain regions and whole genome expression analysis performed by microarray. Principal components analysis revealed region-dependent heterogeneity in microglial transcriptomes and network analysis identified 3 major patterns of gene co-expression underpinning this heterogeneity. Transcriptional networks controlling bioenergetic and immunoregulatory function were the major processes responsible for microglial diversity. Differences in immunophenotype indicated a more immune vigilant state of cerebellar and hippocampal microglia but this phenotype was distinct from conventional activation states. Functional differences in the ability of microglia from different brain regions to sequester bacteria and control replication correlated with the regional pattern of immune vigilance. Comparison with systemic macrophage transcriptomes showed that microglial regional diversity is superimposed upon a core profile distinguishing microglia from non-CNS macrophages. Identified genes and associated bioenergetics and immunological functions driving regional heterogeneity of microglia were greatly consistent throughout the ageing process, however partly amplified suggesting region-dependent kinetics of microglial ageing. Thus, in the absence of age-related neurodegenerative diseases, ageing microglia partially maintain regionally distinct phenotypes, which may become more pronounced with age.

Poster Ref: P2-B-034

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Neuronal activity does not affect Nrf2 protein levels, but can transcriptionally induce known Nrf2 target genes independently of Nrf2 and astrocytes by regulating transcription factors other than Nrf2.

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Nuclear factor E2-related factor 2 (Nrf2) is a transcription factor that controls the transcription of antioxidant genes primarily in astrocytes, providing protection to nearby neurons during oxidative stress. It has been shown that neuronal activity can transcriptionally induce Nrf2 target genes; but whether this induction occurs in neurons or indirectly in astrocytes, and whether it is mediated by Nrf2 or other transcription factors is unclear. Both neuronal activity and the Nrf2 pathway have neuroprotective effects, but it is unknown if these occur by distinct mechanisms.

Here we show that neuronal activity induces Nrf2 target genes in an astrocyte and Nrf2 independent manner.

Neuronal activity was achieved by either promoting synaptic activity or by inducing membrane depolarization in mouse primary neuronal cultures. Neuronal cultures with varying amounts of astrocytes were prepared (mixed (10% astrocytes, 90% neurons), astrocyte enriched (15% astrocytes) or neuronal (<0.2% astrocytes) cultures) to determine the cell specificity of Nrf2 target gene induction by neuronal activity. The effect of neuronal activity on Nrf2 target genes in Nrf2 knock-out (KO) versus wild-type (WT) mixed cultures, and in astrocyte enriched versus neuronal cultures was assessed using real-time quantitative PCR. Protein levels of Nrf2 following neuronal activity was shown by Western blotting and immunocytochemistry.

Nrf2 target genes, such as sulfiredoxin 1 (Srxn1) and system Xc- transporter (XCt), were transcriptionally induced by an Nrf2 activator. Nrf2 target genes were induced by neuronal activity in both WT and Nrf2 KO mixed cultures, as well as in WT neuronal and astrocyte enriched cultures. Nrf2 protein levels were not strongly affected following neuronal activity in astrocytes or neurons.

This shows that Nrf2 target genes can be induced by neuronal activity, independently of both Nrf2 and astrocytes in primary neuronal culture, by transcription factors other than Nrf2. Nrf2 protein levels are not strongly affected by neuronal activity, suggesting that the neuroprotective effects of neuronal activity in culture may be independent of the neuroprotection provided by the Nrf2 pathway.

Poster Ref: P2-B-035

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Subcellular localisation of schizophrenia susceptibility protein ZNF804A in human neurons.

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Genome-wide association studies (GWAS) have been extensively used to identify candidate genes for schizophrenia. One of the first genetic variants achieving genome-wide significance for psychosis was rs1344706 in the zinc finger binding protein 804a (ZNF804a). The gene ZNF804a is highly expressed in the brain and encodes a protein of unknown biological function. The protein is predicted to contain a C2H2 zinc finger domain, suggesting a potential role in the regulation of gene expression through DNA and/or RNA binding. Consistent with this, functional knockdown of ZNF804a in human neural progenitor cells results in the dysregulation of cell adhesion molecules, suggesting a role in neural migration, neurite outgrowth and synapse formation. Critically, these cellular functions are thought to play a critical role in the emergence of schizophrenia. However, the biological function of this gene is currently unknown.

In order to gain an insight into the biological function of the ZNF804a, we have studied the subcellular localisation of the protein in a range of neuronal cell types by immunohistochemistry. Specifically, we have investigated the localisation of this protein in neurons differentiated from a human neural progenitor cell line (CTXOE16) and human induced pluripotent stem cells as well as in primary rat cortical neurons. ZNF804a was found to localise to the nucleus of neuronal progenitor cells, young developing neurons as well as in neurons with a mature morphology, consistent with a role in regulating gene transcription. Remarkably, ZNF804a could also be observed in the soma of neurons indicating an extranuclear localisation. Furthermore, the protein could also be observed in distal portions of MAP2 positive dendrites, where it colocalised with putative synaptic markers. Critically, in mature primary rat cortical neurons ZNF804a was found to localize to dendritic spines, the site of excitatory synapses, and to colocalise with synaptic proteins. These data are the first to provide a detailed characterization of the subcellular localisation of the ZNF804a protein in human neurons. The extranuclear and synaptic localisation of ZNF804a is consistent with a role for this protein in the regulation of RNA, and potential additional cellular functions.

Poster Ref: P2-B-036

Theme: B: Molecular, Cellular and Synaptic Mechanisms

In vitro investigation of the role of M4 muscarinic receptors in hippocampal and cortico-striatal synaptic transmission.

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Both the hippocampus and striatum receive a substantial cholinergic innervation and express multiple muscarinic Ach receptor (mAChR) subtypes reported to alter neural function in multiple ways. Using extracellular recording in coronal brain slices from ~18 week old mice we have revisited the consequences of mAChR activation in these CNS areas. To this end we employed a selective broad-spectrum muscarinic agonist Oxotremorine M (Oxo), as opposed to carbachol, which has been used widely by others but is a mixed muscarinic/nicotinic agonist. Oxo was combined with a number of other muscarinic agents such as positive allosteric modulators (PAMs) and antagonists. In the Schaffer collateral commissural pathway (SCCP) Oxo (0.003 - 10 μM) produced a concentration-dependent depression of excitatory transmission with EC50 of 0.14 μM, this was consistently associated with an increased paired pulse ratio. These effects were fully reversed either upon Oxo washout or by co-application of Atropine (2 μM), no long term Oxo-induced changes in synaptic efficacy (i.e. LTD or LTP) were apparent. In the presence of VU10010 (1 μM), an M4 AChR PAM, EPSP depression produced by 100 nM Oxo was only slightly, but significantly ($P<0.015$) larger (50 ± 4%, n=11) than that elicited by Oxo alone (33 ± 4%, n=11). The Oxo-induced depression produced in the presence of another M4-PAM, VU0467154, (45 ± 5%, n=6) was not significantly different ($P=0.26$) from that produced by Oxo alone. Neither M4 PAM affected basal SCCP synaptic transmission. Antidromic compound action potentials evoked in CA1 pyramidal cells needed much higher concentrations of Oxo (~100 fold) to be depressed and this activity did not appear to be enhanced by an M4 PAM. Corticostriatal transmission (CST) was also depressed 63 ± 7% by Oxo (1 μM) which also enhanced paired pulse ratio. This effect was antagonized by atropine. Preliminary observations indicate that depression of CST produced by 0.1 mM Oxo is enhanced by VU10010.

Poster Ref: P2-B-037

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Deficits in cortical development in a model of intellectual disability highlight an important role for synapse associated protein-102 (SAP-102).

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Synapse-associated protein 102 (SAP-102) is a postsynaptic protein belonging to the MAGUK family and binds to NMDARs. In humans the DLG3 gene encodes SAP-102 and mutations in this gene have been identified in families with a history of X-linked mental retardation (Tarpey *et al.* 2004; Zanni *et al.* 2010). The SAP-102 KO mouse has been shown to exhibit a phenotype consistent with the human condition, including deficits in spatial learning and hippocampal LTP (Cuthbert *et al.* 2007).

Sensory dysfunction is a common feature of ID. Here we study the development of the thalamocortical (TC) input to layer (L4) of the somatosensory cortex, combining anatomical characterisation of TC afferents with whole cell recordings from L4 stellate cells. We find that the relative contribution of NMDA and AMPA receptors during the canonical TC critical period (P4-5) was unchanged but NMDA EPSC decay kinetics were faster in SAP102 KO mice and minimal stimulation identified a reduction in EPSC (msEPSC) amplitude. Although SAP-102 is thought to preferentially bind GluN2B-containing NMDARs, ifenprodil sensitivity was unaltered in SAP102 KO mice indicating a normal contribution of GluN2B-containing receptors. At P8-10, when the critical period has closed in WT animals, no difference in msEPSC amplitude was observed indicating a normalisation of synaptic weight during development. Dual whole-cell recordings during minimal stimulation (Crocker-Buque et al 2014) revealed a reduction in the proportion of L4 neurons contacted by each TC axon. Interestingly SERT immunohistochemistry at P7 revealed normal whisker-related patterning, although TC patches were reduced in size in KO animals. TC axon reconstructions, however, revealed no differences in TC axon arborisation in SAP102 KO animals indicating the decrease in functional connectivity from each axon is not due to a decrease in TCA branching.

Our data demonstrate disrupted NMDA signalling during the critical period for synaptic plasticity and reduced connectivity of TC axons in the somatosensory cortex of SAP102KO mice. These data indicate that Dlg3 mutations alter early stages of development equivalent to the end of the second trimester in humans.

Poster Ref: P2-B-038

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Progress towards the isolation of a novel metabotropic glutamate receptor in annulospiral afferent nerve endings.

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Glutamate is well-established as a central nervous system excitatory neurotransmitter. However, new evidence indicates important functions in the peripheral nervous system, particularly in modulating mechanosensitivity. We use stretch-sensitive annulospiral afferent nerve endings in muscle proprioceptors (muscle spindles) to explore this system. They express synaptic levels of glutamate and glutamate transporters, while exogenous glutamate increases stretch-evoked firing and metabotropic glutamate receptor (mGluR) antagonists markedly inhibit firing, suggesting they express a glutamate receptor. However, its atypical pharmacology most closely matches that of the phospholipase D-coupled mGluR first described 20 years ago in the hippocampus. While the receptor has since been reported in several studies, it has never been isolated or sequenced. As the pharmacology suggests it is the only mGluR in spindles, they are an ideal source of receptor protein.

The rat deep masseter muscle is a rich source of muscle spindles. We developed a method of extracting them to isolate and characterise the atypical mGluR. Adult male Sprague Dawley rats (200 – 450g) were euthanised by CO2 overdose (ASPA 1986, 63/2010/EU) and their deep masseter muscles removed. Both mmunofluorescence of cryosections and fixed (4% formaldehyde) and teased preparations confirmed the mGluR5 labelling reported previously in spindles. In a newly developed technique, spindles were dissociated by collagenase digestion then identified by methylene blue staining. Western blotting for all mGluRs showed only an mGluR5-positive band but at ~102 kDa, not the expected ~150 kDa protein seen in hippocampus. Affinity chromatography confirmed a protein with mGluR5-like immunoreactivity at ~102 kDa. In contrast, Far western blotting with ZCZ-180 – a biotinylated receptor ligand we have developed – labelled a band at ~110 kDa. Moreover, mass spectrometry of hydrophobic proteins found a similar sized protein not matched by any in the Mascot database. These data suggest there are two separate glutamate-binding proteins in spindles, possibly even a novel heterodimer, that may underlie this atypical pharmacology. Further protein isolation and Edman sequencing of these two proteins are planned.

Poster Ref: P2-B-039

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Somatic transposition introduces genetic diversity in *Drosophila* mushroom body neurons.

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Mobile genetic elements can radically alter genome structure, thereby altering gene expression and cellular function. Given that transposons challenge the integrity and stability of DNA, their mobilisation is heavily constrained in the germ line of all higher eukaryotes. However, surprisingly recent findings suggest that transposable elements are active in adult brain tissue of mammals and fruit flies. The impact of these somatic transposition events on the function of neurons remains elusive.

Perrat and colleagues previously reported that transposons are expressed at moderate levels in subsets of memory-relevant neurons in the fruit fly mushroom body (MB). Over 200 insertion events were described that could not be detected in the rest of the brain of the same cohort of animals, or in genetically closely related embryos. These results suggest that the new insertions occurred in somatic cells of individual flies.

To better understand the effects that neural transposition has on an organism, we are investigating the frequency and potential target site preference of somatic insertions by sequencing genomes from a number of different neural cell-types. Our results reveal an even higher number of de-novo transposon insertions than previously described. This high rate of novel insertions was observed in the entire fruit fly MB. In addition, several memory-relevant loci, such as the dunce locus, were disrupted by transposon insertions at multiple positions in different subsets of cells. These findings confirm that the genomes of individual cells in a single brain are highly diverse. I will present my latest data.

Poster Ref: P2-B-040

Theme: B: Molecular, Cellular and Synaptic Mechanisms

The role of the complement system in regulating basal adult hippocampal neurogenesis *in vitro*.

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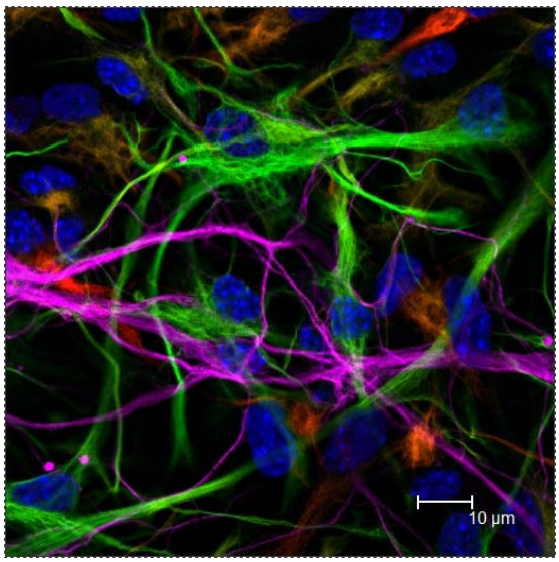
Adult neurogenesis occurs within the subgranular zone of the hippocampal dentate gyrus, where newly generated granule cells are thought to support hippocampal functions such as pattern separation. Mesial temporal lobe epilepsy (mTLE), a chronic, often drug refractory condition, is associated with severely impaired hippocampal neurogenesis. Indeed, learning and memory dysfunction is the commonest neuropsychological effect of mTLE, for which there are currently no pharmacological treatments. Our research investigates the regulatory factors controlling adult neurogenesis, in order to identify target pathways for manipulation and restoration of neurogenesis in the epileptic brain, thereby improving learning and memory deficits.

mTLE is now thought of as a chronic neuroinflammatory condition. Emerging evidence suggests that the complement system may play a role in regulating neurogenesis, both in the epileptic and healthy brain. Several complement components have been demonstrated as either pro or anti-neurogenic under basal conditions, and there is altered expression of complement proteins in resected human mTLE tissue. The specific mechanisms underlying these observations remain unclear however.

To examine the role of complement in regulating basal neurogenesis in the healthy brain, a paradigm for generating primary hippocampal cultures from postnatal mice has been developed. Initial data indicates that in the absence of the pivotal molecule of the complement cascade, C3, there is an increased cell count compared to wild type-derived cultures. This effect appeared to be a consequence of enhanced cell viability in the absence of C3. Furthermore, when cultured as neurospheres, the survival effect in C3 deficient cultures is diminished, which may be attributable to the absence of microglia.

Future work will further examine the mechanisms by which complement affects cell viability in interaction with microglia, before investigating whether complement disrupts neurogenesis in mTLE using resected human mTLE tissue and animal models.



Primary cultured neural precursor cells isolated from the postnatal murine hippocampus. After 5 days *in vitro*, cells were stained using immunocytochemistry with antibodies against nestin (red) to indicate precursor cells, GFAP (green) for astrocytes/radial glia and TUJ1 (magenta) for immature neurons. Cells were also counterstained with DAPI to indicate nuclei (blue).

Poster Ref: P2-B-041

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Multiple measures of oligomeric amyloid-beta at synapses.

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Alzheimer's disease (AD) is characterized by memory loss, insidious cognitive decline, profound neurodegeneration and the extracellular accumulation of amyloid-beta peptide in senile plaques and intracellular accumulation of tau in neurofibrillary tangles. Loss and dysfunction of synapses are believed to underlie the cognitive decline in AD, and oligomeric forms of amyloid-beta have been shown to be toxic to synapses. Using antibody Nab61, which preferentially detects oligomeric amyloid-beta in combination with array tomography, we recently showed that oligomeric amyloid-beta is present at a subset of synapses in brains of both human AD patients and plaque-bearing transgenic APP/PS1 mice. Here, we further characterize synaptic amyloid-beta in APP/PS1 mice using two additional oligomer-detecting antibodies on array tomograms. The presence of amyloid-beta oligomers at synapses is confirmed by immunogold electron microscopy, Forster Resonance Energy Transfer, and Stochastic Optical Reconstruction Microscopy, validating the use of array tomography for examining the synaptic localization of proteins. Our results show that different oligomeric amyloid-beta species colocalize with synapses and highlight the potential of array tomography for testing of aggregation state specific amyloid-beta antibodies in brain tissue.

Poster Ref: P2-B-042

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Reduced seizure like events in neocortical slices prepared using sucrose based artificial cerebrospinal fluid.

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To understand how seizures originate and propagate during the epileptogenic state, it is critical to preserve excitatory and inhibitory neuronal network functions. The presence of inhibitory veto plays a significant role to decrease the speed of seizure propagation in rodent brain slices1. Brain slices used for *in vitro* studies are prepared using either one of the following protocols. In the majority of studies concerning epileptogenesis, cervical dislocation and removal of the brain using a standard artificial cerebrospinal fluid solution (stdACSF). An alternative approach is terminal anaesthesia followed by cardiac perfusion with a sucrose based ASCF (sACSF). Previous work has demonstrated that slices prepared using sACSF demonstrate higher levels of intact GABAA mediated inhibition with implications for the generation of long term potentiation *in vitro*2. We therefore aimed to examine the implications of the differing forms of brain slice preparation for the generation of acute epileptiform activity *in vitro*.

In stdACSF slices the perfusion of zero magnesium (Mg2+[0]) ACSF elicits seizure-like-events (SLEs) which evolved rapidly. SLEs were observed in majority in the stdACSF slices (>80%) in contrast to only few sACSF slices (<20%) exhibited such events. Immunohistochemical staining of slices from both groups demonstrated a reduction in the density of parvalbumin containing interneurons in stdACSF slices. Using multi-electrode arrays, we observed that the propagation speed of stdACSF-SLEs was significantly faster when compared with sACSF-SLEs. In the case of sACSF-SLEs, the antagonism of GABAA receptors increases the mean propagation speed to values comparable to stdACSF-SLEs. We also compared preparation techniques using the 4-aminopyridine (4-AP) model. Our findings in the 4-AP corroborate the results obtained using the Mg2+[0] model. Together these data suggest that the use of sACSF preserves the inhibitory network in cortical slices for *in vitro* studies and can have important implication on network dynamics. We suggest that preparation of cortical slices using perfused sACSF merits serious consideration during *in vitro* epilepsy studies.

1. Trevelyan *et al.*, (2006) J Neurosci. 26(48):12447-55.
2. Kuenzi *et al.*, (2000) J Neurosci Methods. (1-2):117-22.

Poster Ref: P2-B-043

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Pharmacological characterisation of new kainate receptor antagonists

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Introduction: Kainate receptors (KARs) are one of the excitatory L-glutamate gated ion-channels. KARs are widely distributed in the CNS. KARs are tetrameric assemblies of five different subunits GluK1-5. Presynaptically KARs regulate the release of glutamate and γ-aminobutyric acid (GABA) and postsynaptically they modulate fast excitatory synaptic transmission. However, the lack of selective pharmacological tools has hindered progress in the understanding of the functions of specific KAR subunits. Here we characterise the pharmacological properties of two newly synthesised willardine derivatives (UBP3000 and UBP3001) as KAR antagonists.

Methods: Calcium fluorescence assay HEK293 cells stably expressing homomeric GluK1 (Q), GluK2 (Q), and GluK3 receptors were used and compounds were tested using a Ca^{2+} influx assay according to manufacturer's instructions (Molecular Devices, UK). IC50 and Ki values for reference antagonists (UBP310 and ACET) were also monitored. Concentration-response curves were analysed using GraphPad Prism 5.03 software, with slope factor fixed at 1, and top and bottom fixed at 100% and 0% inhibition, respectively.

Results: We found that UBP3000 and UBP3001 are selective antagonists of GluK1 *vs* GluK2 and GluK3 receptors. For GluK1 receptors UBP3000 and UBP3001 had IC50 values of 80 ±21 nM and 171 ± 44 nM, with calculated Ki values of 34±12 nM and 45±14 nM (n=4), respectively. Furthermore, negligible antagonistic activity on GluK2 receptors was displayed by UBP3000 and UBP3001 when tested up to a concentration 100 μM and the % of antagonism was 6.8±0.6%, 3.8±0.5% (n=4), respectively. However, no significant antagonist effects of the willardine derivatives (100 μM) were observed on L-glutamate (400mM) induced calcium influx in GluK3 cells (n=4).

Conclusion: Our results demonstrate that UBP3000 and UBP3001 are novel potent and selective GluK1 antagonists and are potentially useful new tools to study KARs and their involvement in synaptic transmission, neuronal plasticity and development. We anticipate that continued development of compounds in the same series will provide new tools to explore functions of specific subunits of KARs and will contribute to the study of their physiological roles in the CNS.

Theme C: Sensory and Motor Systems

Posters P2-C-001 to P2-C-031

Poster Ref: P2-C-001

Theme: C: Sensory and Motor Systems

Characterization of the receptive fields of looming sensitive neurons in the moth *Manduca sexta* (Sphingidae, Lepidoptera).

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Manduca sexta feeds on the wing, while visually controlling its position in front of flowers it is feeding on. The moth corrects for flower movements in any direction. Visual feedback enabling the animal's positional control is thought to be provided by looming- and motion-sensitive, visual interneurons. We have studied the receptive field properties of these interneurons to find out how they support the moth's feeding behaviour.

During its initial approach to the flower, or when wind moves the flower towards the moth, it will perceive the flower as a looming object. A flower moving away will be perceived as a receding object. The looming and anti-looming (receding) objects create relative motion between the flower and eyes of the moth which may be characterized by radially oriented optic flow vectors. During looming the object grows bigger, the flow vectors point outwards; during anti-looming the object becomes smaller, the flow vectors reverse their direction.

A class of wide-field motion-sensitive interneurons (FFD cells) in the second optic ganglion (medulla) respond to approaching and receding objects. They also respond to outward and inward turning spirals, an illusion of image expansion/contraction consisting of the same looming and anti-looming optic flow vectors. FFD cells are sensitive to both horizontal and vertical wide filed motion stimuli. They exhibit their highest activity (preferred direction, PD) upon either vertical upward or downward motion and to either horizontal inward or outward motion. Motion opposite to the PD results in the lowest activity, wide-field motion in oblique directions elicit intermediate responses.

We have performed intracellular recordings from FFD cells to study their receptive field organization. Several different ways of combining local motion information may result in the cells' capability to detect looming objects. We applied small-field stimuli to determine the local motion and looming sensitivities at several positions within the cells' receptive fields. We find that the cells retain their sensitivity to small field looming and receding stimuli throughout their receptive field and to both horizontally and vertically moving patterns when stimulated locally and thus exhibit position-invariant response properties.

Poster Ref: P2-C-002

Theme: C: Sensory and Motor Systems

Sex-dependent regulation of rat C-fibre activity-dependent slowing in inflammatory pain.

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Background: C-fibres display activity-dependent slowing (ADS), whereby repetitive stimulation (≥1Hz) results in a progressive slowing of action potential conduction velocity, which manifests as a progressive increase in response latency (1,2). Therefore, ADS may limit nociceptive drive to the spinal cord. Ion channels regulated in inflammatory pain have been implicated in ADS (2,3,4), which suggests that inflammation may alter ADS, which could influence central processing of nociceptive information (3). Furthermore, sex differences in pain sensitivity exist (5) yet neither inflammatory pain nor sex differences in ADS have been explored.

Methods: ~P21 rats, of both sexes, were either untreated (control) or received intraplantar CFA injection 2-5 days prior. ADS was assessed in response to ≥1Hz C-fibre stimulation, using compound action potential recording from isolated dorsal roots and whole-cell patch recording of monosynaptic C-fibre eEPSCs from lamina I NK1R+ neurons in spinal slices. Thermal sensitivity was assessed in a separate group of animals.

Results: C-fibre ADS was reduced by CFA in both isolated dorsal roots and in the C-fibre monosynaptic input to lamina I NK1R+ neurons. Strikingly, CFA attenuation of ADS was sex-dependent, occurring in females but not males. Interestingly, ADS in control females was greater than in males but was reduced by CFA to a level that was similar to males. Behaviourally, females showed increased inflammatory thermal hypersensitivity that reflected a larger reduction in thermal pain thresholds from an elevated baseline level.

Conclusions: C-fibre ADS is more prominent in females than males and CFA inflammation reduces C-fibre ADS in females only. These findings predict the elevated pain thresholds and greater inflammatory pain hypersensitivity that we observed in females in response to noxious thermal stimuli *in vivo*. We conclude that sex/inflammation-dependent regulation of C-fibre ADS likely influences pain sensitivity and is therefore a promising analgesic target.

1. Thalhammer, *et al.*, Somatosen Mot Res. 1994;11:pp243-57.
2. de Col, *et al.*, J Physiol. 2008;586:pp1089-103.
3. Mazo *et al.*, Eur J Pain. 2013;17:pp1281-90.
4. Zhu, *et al*,. Neuro-Signals. 2009;17:pp181-95.
5. J.S. Mogil, Nat Rev Neurosci. 2012;13:pp859-66.

Poster Ref: P2-C-003

Theme: C: Sensory and Motor Systems

Neuroanatomical alterations of mild to moderate hearing loss revealed by grey matter morphometry and diffusion tensor imaging.

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Introduction: Hearing loss is considered as one of the most sensory losses in the healthy ageing population that is associated with other audiological (*e.g.* tinnitus) and non-audiological (*e.g.* dementia) disorders. In this study, we investigated the effect of mild to moderate hearing loss on grey matter (GM) morphometry and white matter (WM) integrity.

Methods: Data were obtained using high-resolution magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI). Twenty subjects with mild to moderate hearing loss (MH) and twenty normal hearing (NH) controls were recruited in this study. Voxel-based morphometry (VBM) and tract-based spatial statistics (TBSS) were conducted.

Results: Mild to moderate hearing loss group showed a significant grey matter volume reduction in right temporal lobe, postcentral, supramarginal and angular gyri compared to normal hearing group. White matter integrity was abnormal, with a significant reduction of fractional anisotropy (FA) values in right superior temporal, precentral, middle frontal and occipital gyri in mild to moderate hearing loss subjects comparing to normal hearing controls. Reduced cortical volume and abnormality of white matter integrity were observed in the right versus left hemisphere.

Conclusion: Our results suggest that mild to moderate hearing loss is associated with brain structure atrophy in different auditory and non-auditory brain regions.

Poster Ref: P2-C-004

Theme: C: Sensory and Motor Systems

Investigating the effect of acute tryptophan depletion on central processing of affective and discriminatory touch using fMRI.

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C-tactile (CT) afferents are slowly conducting nerve fibres, present only in hairy skin. CTs are optimally activated by slow, gentle stroking sensations, comparable to those experienced during a caress. CT stimulation activates the posterior insula, but not the somatosensory cortex (SI), leading to the conclusion that these afferents encode affective rather than discriminatory aspects of touch. Serotonin (5-HT) is a key neurotransmitter involved in affective and somatosensory processing. We investigated the hypothesis that acute tryptophan depletion (ATD) would alter central responses to both affective and discriminatory touch.

An amino acid drink to induce ATD was administered to 16 healthy females, with a further 14 females receiving a placebo drink. After 4 hours, participants underwent an fMRI scan, during which time, hairy forearm skin and glabrous fingertip skin was stroked with a pleasant, neutral and unpleasant brush, at a CT optimal velocity of 5 cm/s and a force of 0.22 N. Data analysis was conducted using the Sandwich Estimator (SwE) toolbox for SPM. The design had a between subjects factor of treatment (ATD or placebo), and two within subject factors of location (forearm or fingertips) and valence (pleasant, neutral or unpleasant).

A treatment x valence x location interaction in contralateral SI, reflected a main effect of valence for touch to the fingers in the placebo, but not the ATD group. Additionally, a treatment x location interaction in left orbitofrontal cortex (OFC) was driven by a greater activation following touch to the arm than the fingers in the placebo, but not the ATD group. There was a main effect of location, with discriminative regions; contralateral SI and secondary somatosensory cortex (SII) activated more following touch to the fingers than the forearm. In contrast, affective regions; contralateral posterior insula and anterior cingulate were activated more following forearm touch.

These results are consistent with previous literature proposing CTs encode affective rather than discriminatory touch. In addition, they support the hypothesis that 5-HT has a role in encoding both affective and discriminatory touch.

Poster Ref: P2-C-005

Theme: C: Sensory and Motor Systems

Quantifying morphological and electrophysiological differences in Purkinje cells between species using clustering techniques.

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Purkinje cells are found in the cerebellum of all vertebrates and are notable for their planar dendritic trees and unique, ‘shelved’ organisation. In mammals, birds, and some reptiles, the cells display immense dendritic branching; in other vertebrates, however, the dendritic trees are far simpler. Passive computational models of Purkinje cells from six species have shown that the electrophysiological behaviour of the cells is very similar despite their morphological differences [1]. These similarities suggest that functional aspects of Purkinje cells have been conserved throughout evolution.

In order to find out if the cells can be differentiated by species, different clustering techniques were applied to datasets based on the morphological and electrophysiological features of the cells. One technique used was growing neural gas [2], an unsupervised machine learning clustering algorithm. Principal component analysis was applied to visualise these results given the high dimensionality of the original datasets. To complement this analysis, Ward’s method agglomerative hierarchical clustering was also used to see if similar clusters were formed. Finally, the Euclidean distances between individual cells and their species average were graphed to explore the variation in Purkinje cell morphology and passive physiology both within and between species.

[1] K. Kidd, H. Cornelis, J.M. Bower, D. Polani, N. Davey, V. Steuber: The implications of evolutionary changes in the dendritic morphology of cerebellar Purkinje cells for information processing [abstract]. BMC Neurosci 2013, 14 (Suppl 1): P373.

[2] B. Fritzke: A growing neural gas network learns topologies. in Advances in Neural Information Processing Systems 7, G. Tesauro, D.S. Touretzky, T.K. Leen, Eds. MIT Press, 1995, pp. 625-632.

Poster Ref: P2-C-006

Theme: C: Sensory and Motor Systems

Bridging the gap in brain-computer interface research moving into the real world – a novel distance adaptable steady state visual evoked potential based brain-computer interface.

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Brain-computer interfaces (BCIs) provide a channel which does not depend on the brain's normal output pathway to communicate and control an external device. Steady state visual evoked potentials (SSVEP) based BCIs have the advantage over other EEG based BCI paradigms, in terms of speed, accuracy, commands scalability and user training time required. In the last two decades, SSVEP based BCIs (SSVEP BCIs) have attracted great attention. While most SSVEP BCI studies focus on the improvement of the signal detection and the classification accuracy, there is still a need to bridge the gap of BCI research to the practice in the real world. This study proposes a novel distance adaptable SSVEP BCI paradigm which allows its users to operate the system from a range of viewing distances between the user and the visual stimulator. Unlike the conventional SSVEP BCI where the users can only operate the system when they are sitting in front of the visual stimulator at a fixed distance, in our proposed system, the users can operate BCI at any viewing distance within the range in this proposed BCI. The proposed BCI system can be used by older people with degenerating mobility or by patients with impaired mobility in the care environment to support their independence. Moreover, the system can also be used by healthy people in a smart home or for a game control environment.

This study first investigates the impact of the viewing distance on SSVEP response and compensates the deterioration of SSVEP caused by the change of viewing distance by changing the intensities of the visual stimuli. 10 healthy subjects participated in the experiment to evaluate the feasibility of the proposed SSVEP BCI. Eleven electrodes in the occipital region were selected for EEG acquisition. The visual stimulator comprising 4 red light emitting diodes flickering at 12Hz, 13Hz, 14Hz and 15Hz was presented to the subjects at 4 viewing distances, 60cm, 150cm, 250cm and 350cm. The offline experimental mean classification accuracy across the subjects and the viewing distances was over 75% and demonstrated the feasibility of a distance adaptable SSVEP based BCI.

Poster Ref: P2-C-007

Theme: C: Sensory and Motor Systems

Invariant visual object recognition in the inferior temporal visual cortex: biologically plausible approaches.

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The biological plausibility of two leading approaches to invariant visual object recognition in the ventral visual system is investigated, in order to elucidate some of the fundamental principles of object recognition in the brain. VisNet is a four-layer hierarchical network that uses competitive learning to build feature combination neurons and a temporal trace associative synaptic modification rule to learn transform invariant representations. HMAX is a multiple layer net with simple and complex cell layers alternating. Experiment 1 shows that VisNet performs object classification with random exemplars comparably to HMAX, except that the final layer C neurons of HMAX have a very non-sparse representation (unlike that in the brain) that provides little information in the single neuron responses about the object class. Experiment 2 shows that VisNet forms invariant representations when trained with different views of each object, whereas HMAX performs poorly when assessed with a biologically plausible pattern association network, as HMAX has no mechanism to learn view invariance. HMAX thus relies on subsequent powerful pattern classification mechanisms such as a Support Vector Machine to decode its outputs. Experiment 3 shows that VisNet neurons do not respond to scrambled images of faces, and thus encode shape information. HMAX neurons responded with similarly high rates to the unscrambled and scrambled faces, indicating that low level features including texture may be relevant to HMAX performance. Experiment 4 shows that VisNet can learn to recognise objects even when the view provided by the object changes catastrophically as it transforms, whereas HMAX has no learning mechanism in its S-C hierarchy that provides for view-invariant learning. This highlights some requirements for the neurobiological mechanisms of high-level vision, in order to help understand the crucial underlying principles of invariant visual object recognition in the ventral visual stream of cortical areas. VisNet produced neurons in all these investigations like neurons in the inferior temporal visual cortex.

Rolls,E.T. (2012) Invariant visual object and face recognition: neural and computational bases, and a model, VisNet. Frontiers in Computational Neuroscience 6: 35 (1-70).

Poster Ref: P2-C-008

Theme: C: Sensory and Motor Systems

An overview of cerebellar evolution with a focus on Purkinje Cells: from fish to primates.

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The cerebellum is a structure of the brain that can be found in all vertebrates [1]. Although there are differences in complexity, many features of the cerebellum have been conserved throughout millions of years of evolution. This holds for much of the cerebellar organisation and circuitry in mammals today, including the arrangement of planar Purkinje cells, which receive a large number of parallel fibre connections and input from a single climbing fibre that extends from the inferior olive. There are also similarities between the firing patterns and ion channels of Purkinje cells in mammals [2, 3] and those in reptiles [4] and fish [3].

Here, we review the available literature and discuss the main evolutionary changes in the cerebellum and, in particular, cerebellar cortical Purkinje cells and their excitatory and inhibitory inputs, from fish to modern primates. Most of these changes are found at the level of complexity in the cerebellar structure and in the neurons that populate it, rather than comprising large-scale changes such as the addition or deletion of cerebellar features.

[1] C.C. Bell: Evolution of Cerebellum-like Structures. Brain Behav. Evol., vol. 59(5-6), pp. 312-326, 2002.
[2] R. Llinás, M. Sugimori: Electrophysiological Properties of *In vitro* Purkinje Cell Dendrites in Mammalian Cerebellar Slices. Journal of Physiology, vol. 305(1), pp. 197-213, 1980a.
[3] M.M. de Ruiter, C.I. De Zeeuw, C. Hansel: Voltage-gated Sodium Channels in Cerebellar Purkinje Cells of Mormyrid Fish. Journal of Neurophysiology, vol. 96(1), pp. 378-390, 2006.
[4] J. Hounsgaard, J. Midtgaard: Intrinsic Determinants of Firing Pattern in Purkinje Cells of the Turtle Cerebellum *In vitro*. Journal of Physiology, vol. 402(1), pp. 731-749, 1988.

Poster Ref: P2-C-009

Theme: C: Sensory and Motor Systems

Event related potential correlates of auditory attention in real-life settings.

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Traditional EEG research has established a respectful understanding of the neural correlates of behaviour within highly controlled laboratory settings using reliable and replicable paradigms. Technological advances mean it is now possible to step outside the laboratory with a fully mobile EEG system and using those same paradigms, obtain quality recordings equalling those achieved in meticulous research environments (De Vos *et al.*, 2013; Debener *et al.*, 2012). This study employed a mobile EEG system to collect ERP measures of auditory endogenous attention, using a manual response to a three-stimulus oddball task (two infrequent stimuli; one target, one distractor, each presented at 14% probability) in environments reflecting real-life settings; namely seated (indoors, outdoors); and walking (indoors, outdoors). Data from 18 participants demonstrated that for both the N1 and P3 ERP components there were no discernible differences in attentional processing between each of the recording conditions, however, the oddball paradigm generated significant main effects of the three stimulus tones for each ERP component. Further analysis revealed that processing the infrequent target stimulus in each of the walking conditions resulted in relative attenuation of P3 amplitude in comparison to the seated conditions, and differential N1 modulation to infrequent stimuli in both seated conditions and indoors walking condition that was entirely absent in the outdoors waking condition. Data suggest there are subtle influences on auditory attentional processes which result directly from being outdoors and also, walking. Evidently, when transposing laboratory based interpretations of cognitive processes to real life settings, researchers must first consider the complexity of disentangling cognitive interactions within naturally encountered, stimulus rich environments.

De Vos, M., Gandras, K., & Debener, S. (2013). Towards a truly mobile auditory brain-computer interface: Exploring the P300 to take away. International Journal of Psychophysiology , 91(1), 46–53.

Debener, S., Minow, F., Emkes, R., Gandras, K., & de Vos, M. (2012). How about taking a low-cost, small, and wireless EEG for a walk? Psychophysiology, 49(11), 1449–53.

Poster Ref: P2-C-010

Theme: C: Sensory and Motor Systems

The smoothest contour principle underlying visual information processing in V1.

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Humans are adept at recognizing smooth contours made up of several oriented elements (bars, Gabor patches, etc.) among a noisy background, but we are challenged if the contour is not smooth. The underlying mechanism is commonly modelled with an 'association field' (Field, Hayes & Hess 1993) where elements that form a good (smooth) continuation of each other are strongly associated, but elements which form a poor continuation are weakly associated. Here we show how the smoothness principle leads to many basic features of human psychophysics and contextual tuning of V1 neurons, suggesting that V1 uses smoothness to process visual information.

The idea of smooth continuation can be quantified by finding the spline curve of minimum curvature energy connecting a given element-pair (known as the Elastica Principle). The smoother the curve, the lower the curvature energy. For example, for two perfectly aligned elements, the maximally smooth curve between them is a straight line, and energy is zero. If one element is perpendicular to the other, the curve connecting them needs to be windy, and the associated energy is large.

We develop a neural model probabilistically representing the orientation of an element, combining what the smoothest continuations would be from any neighbouring elements. The contextual tuning of the model's neurons is qualitatively similar to V1 contextual interactions, portraying forms of the association field and surround modulation. The model reproduces several forms of the tilt illusion, where the orientation of a central element is misjudged in the presence of differently oriented flankers. It furthermore performs basic saliency detection, with pop-out effects for differing elements among a homogeneous background, as well as contours among a noisy background.

Poster Ref: P2-C-011

Theme: C: Sensory and Motor Systems

Role of Synj2 in high frequency progressive hearing loss.

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Introduction: Synaptojanin 2 (Synj2) is a phosphatidylinositol phosphatase which removes the 5-position phosphates from phosphoinositides, such as PIP2 and PIP3. It is a key enzyme in the phosphoinositide signalling cascade and in clathrin-mediated endocytosis. We are interested in exploring the effect of Synj2 mutation on the development and function of inner hair cell synapses.

Methods: Synj2 mutant mice (Synj2tm1a(EUCOMM)Wtsi) were generated at the Sanger Institute. Auditory Brainstem Response (ABR) measurements were recorded from ketamine/xylazine anaesthetised mice at 2, 4, 6, 8, 12 and 14 weeks old in response to click stimuli and tone pips ranging from 6-42kHz. The morphology of the nerve endings in the organ of Corti was studied in whole mount preparations labelled with anti-neurofilament antibody and CtBP2 antibody was used to label ribbon synapses. Specimens (mutant n=5, control n=4) were examined at 10% intervals along the length of the cochlear duct using confocal microscope.

Results: Synj2tm1a mutant mice showed normal ABR thresholds, which might be due to incomplete inactivation of transcription in the tm1a allele. Therefore, we crossed the Synj2tm1a mutant mice to CMV-Cre mice in order to delete the critical exons (9-11) and generate the Synj2tm1b mutant allele. Mutant mice were tested at 2 weeks by ABR and they had normal thresholds, but ABR recordings from Synj2tm1b mutant mice from 4 weeks showed progressive increase of thresholds for frequencies higher than 30 kHz in comparison to the littermate controls. X-gal staining on sections of inner ear revealed that Synj2 is expressed in the spiral ganglion, organ of Corti and Claudius' cells. Furthermore, we investigated the morphology of nerve terminals in 4 week old Synj2tm1b mice. We observed swelling of nerve fibres under inner hair cells in mutant mice.

Conclusions: ABR measurements showed that Synj2tm1b mutant mice have normal thresholds at 2 weeks, while they lose high frequency sensitivity from 4 weeks onwards. This suggests that some defects occur during that window of time. The Synj2tm1b mice are a useful tool to improve our knowledge of mechanisms underlying high frequency progressive hearing loss.

Poster Ref: P2-C-012

Theme: C: Sensory and Motor Systems

Structural connectivity of motor pathways in Parkinson's disease.

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Current treatments for Parkinson's disease such as dopaminergic medication and surgical procedures may cause significant side effects. Hence there is an increasing need to develop effective non-invasive interventions that reduce side effects and the need for medication. Recently, real time functional magnetic resonance imaging Neurofeedback (RT-fMRI-NF) training has shown to improve symptoms of neurological and psychiatric diseases. With this procedure patients are trained to active specific regions of the brain with the aim to reduce their symptoms and improve clinical outcomes. However, the mechanisms underlying the therapeutic effects of neurofeedback remain poorly understood. The present study investigated whether neurofeedback training with the aim to activate motor regions in Parkinson's disease would lead to plastic changes in white matter connections of the motor network. Diffusion tensor imaging (DTI) tractography which uses the property of random motion of water molecules to detect differences in white matter microstructure and give anatomically plausible white matter tracts was performed to detect differences between 24 age-matched PD patients and 26 healthy controls (HC). We found novel results where there was selective increase in fractional anisotropy (FA) and axial diffusivity (AD) in the motor tracts (right corticospinal tract, right and left thalamus-motor cortex tract and right supplementary motor area-putamen tract, corrected for multiple comparisons using Bonferroni correction, $p<0.05$) of PD patients compared to the healthy controls. We speculate that this may be due to compensatory mechanisms that may indicate preserved neuroplasticity in Parkinson's disease. However, further work and future studies are much needed for better interpretation and understanding before making any strong conclusions.

Poster Ref: P2-C-013

Theme: C: Sensory and Motor Systems

Cerebellar neurons encode locomotion-related movements in mice navigating in a virtual reality environment.

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The cerebellum plays a key role in motor behaviour, sensorimotor learning and control. Electrophysiological studies in rodents and non-human primates have shed light on how the activity of single neurons of this structure can allow us to learn and execute finely coordinated movements. Evidence from more recent imaging investigations in mice suggests that topically segregated populations of cerebellar neurons become active during locomotion (Ozden *et al.*, 2012, PLoS One, vol.7 issue 8 e42650). To date, however, little is known as to how these networks of neurons function and communicate to coordinate locomotive movements. To this end, we use a novel experimental paradigm comprising high-density silicon electrode arrays to record activity of multiple cerebellar neurons from locomotion-related areas in behaving mice.

We recorded from movement-sensitive populations of neurons in lobule IV-V of cerebellar vermis of mice navigating in a virtual reality environment. Activity of isolated units was found to change according to locomotion direction, speed and stride pattern of the mouse. Three neuronal response profiles were found: 1- cells whose firing rate is correlated with locomotion speed and acceleration; 2- cells that modulate their activity with respect to the yaw rotation of the spherical treadmill on which the animal is head-fixed; 3- cells that burst in synchrony with stride frequency. We are further characterising the activity of these cells with respect to their electrophysiological properties.

Our approach enables us to identify the functional properties of populations of cerebellar neurons in animals during virtual reality behavioural tasks to probe computational principles of sensorimotor control.

Poster Ref: P2-C-014

Theme: C: Sensory and Motor Systems

Variability in axon initial segment location of spinal motoneurones.

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The axon initial segment (AIS) is the region of the neurone where action potentials are initiated. Neuronal excitability can, therefore, be partly determined by the structure and location of the AIS. In our previous investigations of AISs of spinal motoneurones in injury/disease models we noticed a large range with respect to distance from the cell body, even in control groups. Our aim was, therefore, to identify factors explaining this variability.

Using immunohistochemistry, we labelled Nav1.6 or AnkG (AIS markers) and ChAT (motoneurone marker). To determine the influence of sex we compared AISs in 250 day old male and female C57BL/6J mice. No significant differences were found in any of the parameters (length, width or distance from soma, n=177, 9 mice). To test effects of age, we compared AISs in adult male mice (300 days) with geriatric mice (600 days). Subtle differences were found with respect to length and width ($p=0.0001$, n=537, 15 mice) but not with respect to distance from the cell body.

Thus, the large range with distance most likely represents a functional difference. Spinal motoneurones are recruited in an orderly sequence, starting with the small, slow motoneurones before the larger, faster motoneurones. We hypothesised that this may be determined by AIS location. As slow motoneurones of rats preferentially express the SK3 channel (Deardorff *et al.* 2013) we labelled SK3 to classify slow *vs* fast motoneurones. There were no significant differences between the two groups. We did observe, however, that a population of small diameter ChAT positive neurones lacking C-boutons (presumably γ-motoneurones) had significantly shorter ($P<0.0001$), thinner ($P<0.0001$) AISs (n=357, 8 rats) which were significantly farther from the soma ($P<0.0001$, n=353, 8 Wistar rats). Even when excluding this population, a large range with respect to distance still persisted. One confound is that we have so far ignored possible differences between groups of motoneurones innervating different muscles - a hypothesis we are currently testing.

Reference:

Deardorff AS *et al.* Expression of postsynaptic Ca2+-activated K+ (SK) channels at C-bouton synapses in mammalian lumbar motoneurons. J Physiol. 2013 Feb 15;591(Pt 4):875-97.

Poster Ref: P2-C-015

Theme: C: Sensory and Motor Systems

The role of synaptic depression in a simple neuronal network with reciprocal inhibition.

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Short-term synaptic plasticity is widely found in many areas of the central nervous system. In particular, it is believed that synaptic depression can act as a mechanism to allow simple networks to generate a range of different firing patterns. The locomotor circuit in hatchling *Xenopus* tadpoles is an excellent place to understand such basic neuronal mechanisms. Depending on the nature of the external stimulus, tadpoles can generate two distinct types of motor activity: swimming when touched and slower, stronger struggling movements when held. During swimming, spinal neurons fire single spikes at 10 to 25 Hz, alternating between both sides of the spinal cord. During struggling, they fire high frequency (100 Hz) alternating bursts. The alternating bursting in struggling is thought to be governed in part by firing-frequency-dependent synaptic depression. We investigate this idea by studying the dynamics of a simplified network consisting of two rhythmically active, reciprocally inhibitory neurons of the tadpole spinal cord. We find that the increased inhibitory firing frequency characteristic of struggling is accompanied by a strong inhibitory depression that provides a mechanism for burst termination by allowing phase transition. Varying parameters of the depression model changes the firing properties of the alternating bursting such as burst duration, inter-burst-interval and burst frequency. This result is in line with the view that synaptic depression increases the number of possible activity patterns of networks allowing them to contribute to multiple tasks.

Poster Ref: P2-C-016

Theme: C: Sensory and Motor Systems

Modulation of pain-associated hyper-excitability at central synapses of capsaicin-sensitive nociceptors.

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TRPV1-expressing (capsaicin-sensitive) afferents correspond largely to peptidergic nociceptors, which play an important role in both acute pain and chronic hyper-sensitive pain states. Investigation of processes that can modulate function of their early central synapses in spinal dorsal horn could point the way to novel analgesics for chronic pain. We have developed a new method to quantify receptor-evoked Ca^{2+} fluorescence responses of ex vivo synaptic preparations and use it here to measure capsaicin-evoked responses in dorsal horn from control and pain state animals.

Synaptoneurosomes (re-sealed presynaptic and closely apposed postsynaptic compartments) were prepared from dorsal lumbar spinal cord of male Sprague-Dawley rats, under conditions designed to maintain functional integrity, and loaded with a no-wash Ca^{2+} fluorophore (Calcium 5). Capsaicin or other agents (including ionomycin as a positive control) were added *in vitro* and responses measured by fluorometric plate reader.

Responses to capsaicin showed concentration-dependent increases from 0.2-10 microM, were 5-6 fold greater in dorsal than in ventral horn and were largely reversed by the TRPV1 antagonist AMG9810 or presynaptically acting tetanus toxin. In addition the responses were inhibited by antagonists of AMPA- or NMDA-type glutamate receptors, consistent with glutamatergic transmission from capsaicin-activated presynaptic terminals. Agents selective for several distinct subtypes of GluN2 subunit showed differential ability to inhibit capsaicin responses.

We further explored the effects of endogenous analgesic mechanisms. *In vitro* addition of mu (and to a lesser extent delta) opioids strongly attenuated capsaicin responses. In a model of chronic inflammatory pain (intraplantar Complete Freund's Adjuvant), *ex vivo* responsiveness to capsaicin was increased in a manner completely reversed by NMDA receptor antagonists. This inflammation-induced hypersensitivity at TRPV1 afferent central synapses was strongly attenuated by prior *in vivo* administration of the TRPM8 agonist, icilin (200 microM topical to hindpaws, 15 min).

These observations reveal quantifiable actions of established or novel analgesic targets impacting on central synapses of TRPV1-expressing nociceptors.

Poster Ref: P2-C-017

Theme: C: Sensory and Motor Systems

The spatial distribution of spike-related slow potentials in macaque primary motor cortex.

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Introduction: A recent study [1] in primate motor cortex has described features in the low-frequency local field potential (lf-LFP) that are time-locked to neuronal firing (so-called 'spike-related slow potentials', SRSPs). SRSPs associated with a single neuron exhibited considerable variation in shape, amplitude and polarity across LFPs recorded on other electrodes. We speculate that this variability reflects spatially-distinct spike-related sources arising from synaptic currents associated with the network in which the neuron is embedded.

Aims: We examined the spatial distribution of SRSPs in order to investigate their physiological basis and to inform the design of recording arrays optimised for extracting signals for LFP-based Brain-Machine Interfaces (BMIs).

Methods: We recorded from 12 moveable microwire electrodes implanted in the primary motor cortex of a macaque. In addition, we used two linear microelectrode arrays (LMAs; 16 channels, 0.5mm spacing), implanted through the bank of the central sulcus and the convexity of the pre-central gyrus respectively, to provide a spatial profile of the LFP.

Results: We calculated SRSPs by fitting a multiple-input multiple output model relating firing rates to lf-LFPs [1]. Principal Component Analysis (PCA) suggested that the variability in SRSP waveform was greatest across microwires and across the sulcal LMA, while the gyral LMA exhibited stereotyped SRSPs. In general >90% of the variability of SRSPs recorded from the gyrus was explained by a single PC. Across both LMAs and microwire recordings, three PCs were able to capture ~98% of the total SRSP variability.

Conclusions: These findings suggest that using electrodes targeting specific depths within the bank of the central sulcus may minimise the redundancy (hence maximise the information content) of the recorded lf-LFPs. A reduction in the number of channels required, alongside our use of low frequency signals, may enable recording and signal-processing using low-power electronics. This has important implications for the development and miniaturisation of robust, low-power BMIs for human patients.

[1] Hall TM, Nazarpour K, Jackson A (2014), Real-time estimation and biofeedback of single neuron firing rates using local field potentials. Nat Comms, DOI: 10.1018/ncomms6462.

Poster Ref: P2-C-018

Theme: C: Sensory and Motor Systems

Perceiving and acting upon weight illusions in the absence of somatosensory information.

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When lifting novel objects, the fingertip forces employed are influenced by a variety of visual cues such as object volume and apparent material. This means that heavy-looking objects tend to be lifted with more force than lighter-looking objects, even when they weigh the same amount as one another. These expectation-induced errors are rapidly corrected, and lifters rapidly adapt their forces to reflect objects' actual mass. Expectations about object weight based on visual appearance also influence how heavy an object feels when it is lifted. For example, in the 'size-weight illusion', small objects feel heavier than equally-weighted large objects. Further, in the 'material-weight illusion', objects which seem to be made from light-looking materials feel heavier than objects of the same weight which appear to be made from heavy-looking materials. Here, we investigated the degree to which peripheral somatosensory information contributes to these perceptual and sensorimotor effects in size and material weight illusion paradigms. We examined perception of heaviness and fingertip force application over repeated lifts of identically-weighted objects which varied in size or material properties in IW, an individual with peripheral deafferentation (*i.e.*, a complete loss of haptic and proprioception feedback). Although IW showed little evidence of sensorimotor prediction based on how heavy each object appeared to be, he experienced both the size and material weight illusions.

Poster Ref: P2-C-019

Theme: C: Sensory and Motor Systems

Optical manipulation of neuronal gain modulation in abstract and detailed models: morphology matters.

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The interplay of excitatory and inhibitory activity in neuronal populations is finely regulated within cortical layers. One of the key regulatory mechanisms is gain modulation, in which the amplitude of response changes while the cell's selectivity remains unaffected. However, as synaptic locations are located throughout the dendritic arbor and dendritic integration is non-linear, it remains unclear how gain is modulated as a function of competing excitatory and inhibitory input.

For investigating and manipulating this balance of activity, optogenetics is a powerful tool due to the fine temporal and spatial precision it provides. Furthermore, due to the development of excitatory (*e.g.* channelrhodopsin ChR2) and silencing opsins (*e.g.* halorhodopsin NpHR) which respond to different activation wavelengths, dendritic regions can be optically co-activated independently but simultaneously. This provides the opportunity to examine how excitatory and inhibitory inputs for differing spatial and temporal patterns of activation modulate gain in individual neurons.

We investigate this relation by testing optical activation in abstracted neuron morphologies that include models of ChR2 and NpHR. By extending a simple ball-and-stick model, we created a family of neural morphologies that varied in polarity and branching of the dendritic trees. External driving input is provided as current injection or as multiple synaptic-like events at locations on dendrites, rather than the soma, to mimic inputs for both *in vitro* and *in vivo* scenarios. Using these models, we find that dendritic morphology strongly indicates a neuron's capacity for gain modulation, whereby neurons with branched dendritic arbors are better able to modulate their input over a range of input conditions. We confirm these trends using detailed biophysical models of cortical pyramidal cells (PC) and hippocampal stellate cells, and find in PCs that simultaneous activation in both apical and basal dendrites are necessary for modulating gain. Finally, from these results we identify improved experimental illumination strategies that are tailored to neuronal morphology and highlight the importance of deep-tissue light penetration to ensure whole cell illumination.

Poster Ref: P2-C-020

Theme: C: Sensory and Motor Systems

Novel signals for brain-machine interfaces: exploiting cyclical low-frequency cortical dynamics.

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During upper-limb movement, multichannel local field potentials (LFPs) in macaque motor cortex show cyclical activity phase-locked to limb submovements at ~3 Hz [1]. We previously presented a brain-machine interface (BMI) controlled by features extracted from cyclical low-frequency LFP dynamics in a single hemisphere [2]. Here we present the results of a bimanual/bi-hemispheric experiment, and compare methods of feature extraction from multichannel LFPs.

A monkey performed a visually-guided bimanual task in which 2-D cursor position was controlled by the isometric flexion torque from each wrist (Figure 1a). We recorded LFPs from bilateral primary motor cortices. To extract BMI control signals, we calculated two instantaneous control signals (AV1 and AV2) according to two different methods:

i) As previously [2], we used “jPCA” to explicitly find two planes exhibiting cyclical dynamics. The control signals were calculated as the areal velocity swept out by the high dimensional LFP trajectory projected onto each of these planes.

ii) For each pair of principal components extracted from the high-dimensional LFP we calculated an areal velocity signal, and then performed dimensionality reduction using factor analysis to yield two control signals.

To assess the suitability of these methods for producing BMI-control signals, we calculated (offline) the receiver-operating characteristic of each signal for the classification of left *vs*. right limb movement. Both ‘dynamics-based’ approaches out-performed classification based on LFP power, and worked even when classification was not possible using LFP power.

Finally, in a series of biofeedback BMI experiments (Figure 1b), we showed that the subject was quickly able to control the position of the cursor in 1-D using the signal AV1−AV2.

In conclusion, the use of areal velocity (which takes into account the dynamics of multichannel LFP data) can provide suitable control signals for use in BMIs, and may offer a simple, robust and low-power alternative to spike-based or power-based decoding approaches.

1. Hall *et al.* (2014) A common structure underlies low-frequency cortical dynamics in movement, sleep and sedation. Neuron.
2. Hall *et al.* (2013) A new brain-machine interface using low-frequency cortical dynamics. SfN 2013 poster.

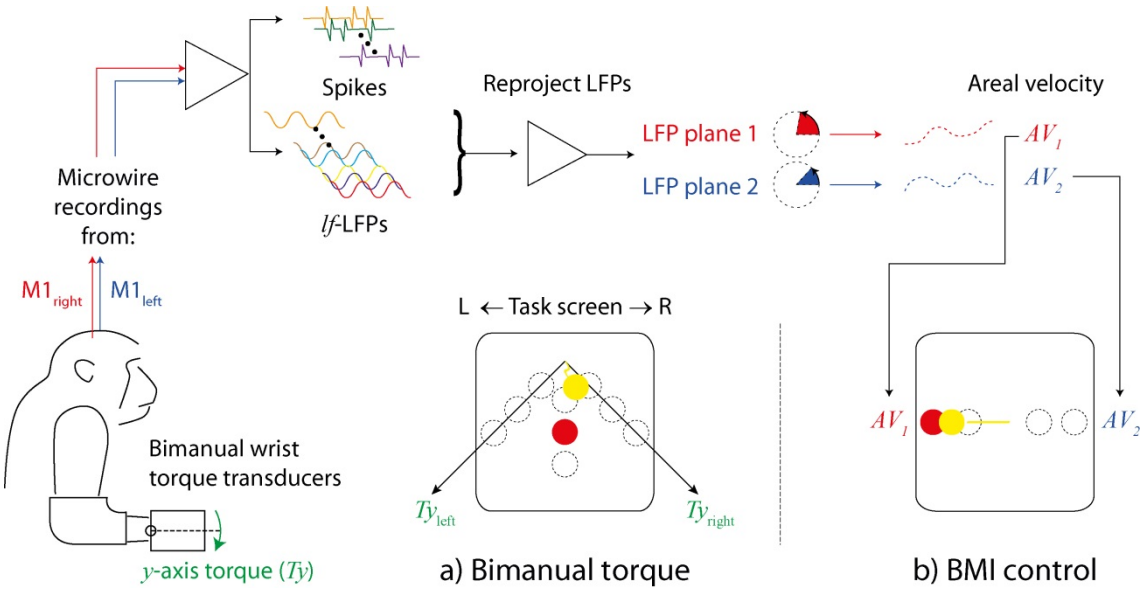

Figure 1: Illustration of (a) the 2-D bimanual torque task and (b) the 1-D areal velocity-controlled BMI task.

Poster Ref: P2-C-021

Theme: C: Sensory and Motor Systems

An emerging role for the endocannabinoid system in regulating hatchling *Xenopus laevis* locomotion.

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The endocannabinoid system has known involvement in many processes in the central nervous system such as appetite, sleep, learning and memory, motor control and at a fundamental level synaptic plasticity. The *Xenopus laevis* tadpole is a widely used locomotion model with a well characterised neural network controlling locomotor behaviour. To date there is no evidence suggesting a role for an endocannabinoid system in modulating locomotion in *Xenopus laevis*, despite compelling evidence for a role in other locomotor models e.g. lamprey. Using ultra slow motion recording (400-1200fps) of evoked swimming in *Xenopus laevis* tadpoles, we demonstrate evidence of a modulatory role for the endocannabinoid system during rhythmic locomotion *in vivo*.

Tadpoles' spinal cords were exposed to either the endogenous cannabinoid N-arachidonoylethanolamine (Anandamide AEA; 50μM) or the cannabinoid receptor 1 (CB1) antagonist/inverse agonist AM-251 (50μM) for 20 minutes. Tadpoles were then transferred to a 10cm petri dish containing swimming solution and left for 10 minutes to equilibrate. Swimming was then initiated by a gentle stroke with a hair loop to the trunk of the body and the resultant swimming response filmed using a Nikon 1 V1 camera. A detailed analysis of the frequency of swimming was performed. Inhibition of CB1 receptors with 50μM AM-251 decreased swimming frequency by 8.7% (n=48) compared to control (SEM =±0.33911%, n=46, $P < 0.001$). Conversely application of AEA (50 μM) had no significant effect on locomotion (SEM =±0.41021%, n=50, $P > 0.05$).

This data provides the first evidence of a role for endocannabinoids in the locomotor network of the hatchling *Xenopus laevis* tadpole. The simplest explanation for these results is that there is endogenous release of cannabinoids which act within the Central Pattern Generator (CPG) and have a role in maintaining swimming frequency. Further study is required to determine the extent of endocannabinoid involvement and the precise locations of the CB1 receptor in the CPG network.

Poster Ref: P2-C-022

Theme: C: Sensory and Motor Systems

Neurofeedback training in Huntington's disease: enhancing neural plasticity using real-time fMRI neurofeedback training.

Marina Papoutsi[1], Nikolaus Weiskopf[2], Douglas Langbehn[3], Ralf Reilmann[4], Geraint Rees[2,5] and Sarah Tabrizi[1]

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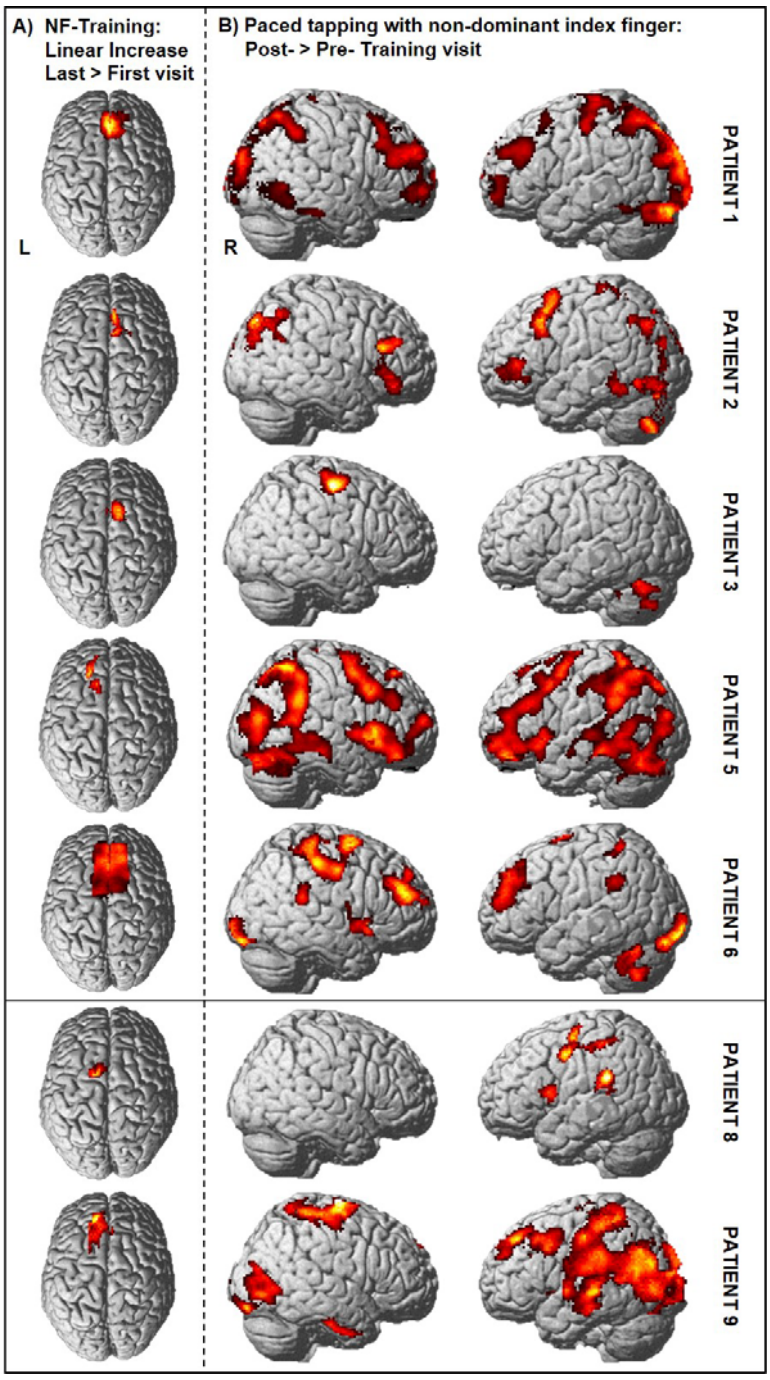
Early stages of Huntington's disease (HD) are characterised by widespread atrophy, as well as changes in brain activation and connectivity. Recent work shows that it is possible to regulate brain function and improve behaviour pharmacologically or non-invasively using neurofeedback training (Bakker *et al.*, 2012; Subramanian *et al.*, 2011). The aim of our study was to use real-time fMRI (rt-fMRI) neurofeedback training in HD patients to regulate the activity of specific brain regions, such as the premotor cortex (PMC), whose function is affected by the disease and is linked to cognitive and motor impairment (Klöppel *et al.*, 2009).

Ten HD patients took part in the study and attended: 1 baseline, 3-4 neurofeedback training sessions and 1-2 post-training visits. The neurofeedback training sessions consisted of a functional localiser run (fist clenching) to delineate the PMC, followed by 4 neurofeedback training runs. Neurofeedback was presented visually as a red bar whose height represented PMC activity compared to baseline. Baseline and post-training visits comprised motor and cognitive assessments sensitive to HD progression (Tabrizi *et al.*, 2009, 2011, 2012, 2013).

Seven patients successfully learned to regulate PMC activity showing significant linear increases in their PMC activation from the first to the last training visit during "regulate" blocks compared to "rest" (see Figure 1A). They also showed increased motor network activation following training compared to before in a paced finger tapping task without explicit neurofeedback (Figure 1B).

We provide evidence that rt-fMRI neurofeedback training can be used to train HD patients to regulate their brain activity. Following training we observed changes in motor network activity, even when the patients were not explicitly up-regulating their premotor cortex activity. Neurofeedback training is therefore feasible in HD and holds potential as a non-invasive, low-risk treatment that could be used as an adjunct to other disease modifying therapies.



Single subject results for 7 learners: (A) linear increase within the PMC ROI from the first to the last neurofeedback training visit (small volume correction voxel $p<0.001$ uncorr., cluster $p<0.05$ FWE corr.). (B) Increase of brain activation during paced tapping (*vs* rest) after training *vs* before without neurofeedback (whole-brain threshold voxel $p<0.001$ uncorr., cluster $p<0.05$ FWE corr).

Poster Ref: P2-C-023

Theme: C: Sensory and Motor Systems

Identification of novel agonists of human strychnine sensitive glycine receptors.

Karen Dowers, Catrina Kerr, Daniel Baptista-Hon and Anthony Hope

University of Dundee

The strychnine sensitive glycine receptor (ssGlyR) is the principle inhibitory ligand-gated receptor ion channel expressed in the spinal cord. There is extensive evidence from both pharmacological data and observations from *in vivo* models of pain, supporting the involvement of inhibitory glycinergic systems in the control and modulation of pain processing. For example, ssGlyR expression in the dorsal horn of the spinal cord is reduced in the rat sciatic nerve constriction injury model of neuropathic pain. Furthermore, in a range of mouse models of chronic pain, intrathecal administration of selective GlyT1 (Org 25935) and GlyT2 (Org 22543) glycine uptake inhibitors, produced prolonged reversal of mechanical allodynia and this effect was abolished by knockdown of ssGlyR. Whilst the contribution of individual glycine receptor subtypes to pain is still being investigated, knockout mice which lack expression of the α3 subunit of the ssGlyR exhibit sensitisation to peripheral inflammation and pain. In addition, ssGlyRα2 subunit knockout prolongs mechanical hyperalgesia in a mouse model of inflammation and may impact on the resolution of inflammatory pain. Enhancing glycinergic transmission by activation or modulation of ssGlyR therefore represents a validated target for the treatment of chronic pain.

Here we report the generation of a stable cell line expressing homomeric ssGlyRα3 cells and the development of a high throughput cell based screening assay to identify novel receptor agonists to target chronic pain. The assay was employed to screen 21,205 compounds from the Drug Discovery Unit (DDU) small molecule collection. 225 active compounds were progressed for potency determination and 45 hit compounds displaying pEC50 values greater than 4.6 identified. Of these, 39 compounds were re-purchased along with 6 commercially available analogues. In addition, 25 further analogues were also selected from the remainder of the DDU compound library. Following an assessment of the potency of all 70 selected compounds, a total of 12 compounds were confirmed as hits capable of activating the ssGlyRα3 receptor.

Poster Ref: P2-C-024

Theme: C: Sensory and Motor Systems

WBP2 is required for normal innervation of cochlear inner hair cells and crucial for hearing in both mice and humans.

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WBP2 encodes the WW domain-binding protein 2 that acts as a transcriptional coactivator for estrogen receptor alfa (ESR1) and progesterone receptor (PGR).

Wbp2-deficient mice were produced as part of the Wellcome Trust Sanger Institute Mouse Genetics Project and screened for hearing impairment. Auditory Brainstem Response (ABR) thresholds were raised at high frequencies as early as 4 weeks of age in the Wbp2-deficient mice and progressively increased and extended to lower frequencies by 14, 28 and 44 weeks old, indicating progressive hearing loss.

While the gross and cellular structure of the Wbp2-deficient mouse middle and inner ears showed no obvious damage or degeneration up to 30 weeks old, confocal imaging performed at 2, 4 and 8 weeks showed swollen nerve endings below inner hair cells, which is a sign of glutamate excitotoxicity. Moreover, ribbon synapses were distributed more widely around the basolateral membrane of inner hair cells in the mutants, and showed abnormal co-localisation of pre- synaptic markers relative to post-synaptic markers. We assessed pre-synaptic function of single inner hair cells using capacitance measurements as an indication of neurotransmitter release, and this was normal in the mutants. Immunofluorescence and qRTPCR indicated a key role for Wbp2 in controlling the expression of scaffolding postsynaptic proteins such as Psd-95 and Shank3 *via* transcriptional regulation of estrogen and progesterone receptors. Finally, mutations in Wbp2 were found in a deaf child, supporting a role for WBP2 in human deafness.

This study describes a new gene involved in the molecular pathway linking hearing impairment to hormonal signalling in mice and in humans, and provides new therapeutic targets.

Poster Ref: P2-C-025

Theme: C: Sensory and Motor Systems

Glial-derived adenosine provides negative feedback on murine spinal locomotor networks.

David Acton and Gareth B Miles

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Although glia can both respond to neuronal activity with elevations in cytosolic Ca^{2+} and release neuromodulators in a Ca^{2+}-dependent manner, the importance of gliotransmission in behaviour remains uncertain. In this study we stimulated glia using protease-activated receptor-1 (PAR1) during ongoing activity of the spinal locomotor central pattern generator (CPG), the output of which is directly relevant to behaviour. PAR1 is preferentially expressed by astrocytes in the brain and has been used to stimulate Ca^{2+} signalling in cortical astrocytes.

We first used immunohistochemistry to show that PAR1 expression is restricted to glia in the mouse spinal cord. PAR1 colocalised with the astrocyte marker GFAP but not with the neuronal marker MAP2 (n=3), supporting its use to selectively stimulate spinal glia. We next investigated the effect of glial stimulation during locomotor-related activity recorded from spinal cords isolated from P1-4 mice. Application of the PAR1-specific agonist TFLLR (10 μM) caused a transient reduction in the frequency of rhythmic bursting (11.6±3.1%, n=10). The effect of PAR1 activation was blocked by theophylline (20 μM, n=10), a general adenosine receptor antagonist, and by the A1-subtype antagonist DPCPX (50 μM, n=10), but not by the A2A antagonist SCH58261 (25 μM, n=10). The effect of PAR1 activation was also blocked by the ecto-ATPase inhibitor ARL67156 (50 μM, n=11). Together these data indicate that glia release ATP when stimulated, and that this ATP is degraded to adenosine that then acts on neuronal A1 receptors. These data are consistent with our previous finding that adenosinergic modulation of the locomotor CPG is lost following glial ablation.

Finally, we found evidence that glia release ATP-adenosine in a manner dependent on CPG activity. We generated different levels of network activity by varying the concentration of NMDA used to stimulate bursting and applied DPCPX to reveal the effect of endogenous adenosine. The change in frequency of locomotor-related bursting upon DPCPX application increased from 3.1±4.2% with 0 μM NMDA to 23.8±2.8% with 5 μM NMDA. Together these results suggest glia respond to neuronal activity with release of ATP-adenosine, providing negative feedback to regulate the output of spinal motor networks.

Poster Ref: P2-C-026

Theme: C: Sensory and Motor Systems

Using effective connectivity analysis of combined EEG-fMRI data to detect signal propagation in the human visual pathways.

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Despite a long history of research studies on the visual system, the spatiotemporal dynamics of signal propagation along the human visual pathways is yet to be validated in an integrated way. In this work, we use an extended thalamocortical model of dynamic causal modelling approach to trace the underlying neural circuit dynamics of pattern-reversal visually evoked potentials (VEPs) extracted from concurrent EEG-fMRI data.

7 key brain regions were identified by EEG inverse problem aided by fMRI spatial priors from the VEPs of 12 subjects: thalamus area (TA), left/right primary visual cortices (L/RVC), left/right posterior parietal (L/RPP), and left/right inferior temporal (L/RIT) areas. Optimal forward-backward model architecture consistent with the hierarchy of visual processing was selected, which allowed for forward connection from TA to VCs and reciprocal connections between VCs and higher cortical areas (*i.e.* PPs and ITs) on the ipsilateral side. Based on the data-driven model, we were able to quantify the timing of signal propagation in the dorsal and ventral visual pathways. Under Bayesian inversion, we performed an effective connectivity analysis on the group average data, and found greater connectivity strength from VCs to PPs than to ITs, suggesting higher level of information transfer along the dorsal than ventral pathway during the pattern-reversal task. From correlation among extrinsic connections, we also found symmetrical propagation from TA to VCs and from VCs to PPs, but asymmetrical signal propagation from VCs to ITs.

In this work, we have shown that the simple VEP task activates the dorsal pathway while suppresses the ventral pathway. This suggests a higher priority in processing visual spatial information than object identification. Moreover, the model showed asymmetry of signal propagation in the ventral pathways. Finally, this study quantifies for the first time signal timing in the human visual pathways. Similar modelling approach could be used to elucidate the spatiotemporal signal propagation in the human visual system and related cognitive processes, or its disruptions in brain disorders.

Poster Ref: P2-C-027

Theme: C: Sensory and Motor Systems

Endogenously released dopamine modulates spinal locomotor output in *Xenopus* tadpoles.

Laurence Picton and Keith Sillar

University of St Andrews

Biogenic amines, such as dopamine (DA), modulate the synaptic and intrinsic properties of neurons in locomotor networks to accommodate rhythms with different speeds and intensities. We have previously shown that in embryonic and early larval *Xenopus* tadpoles, exogenously applied DA acts directly on D2-like DA receptors in spinal CPG neurons to open a GIRK-like potassium channel that reduces the excitability of the swim network. As a result, sensory evoked swimming is slower, weaker, shorter in duration and requires a larger amplitude sensory stimulation. Here we used whole-cell patch clamp recordings to explore the effects of DA and the D2-like receptor agonist quinpirole on the firing properties of CPG neurons during fictive swimming. Exogenously applied DA (50-100 μM) reduced the firing probability of CPG neurons during ongoing swimming. Similarly, the D2-like receptor agonist quinpirole (25 μM) also reduced the firing reliability of recorded cells during swimming. Our intracellular solution contained 0.1% neurobiotin, enabling us to use cell anatomy to determine neuron classes. A number of the neurons used in experiments included clearly identified commissural interneurons (cINs) and motoneurons (MNs). The firing reliability of cINs has previously been shown to dictate the overall frequency of the swimming rhythm in *Xenopus* tadpoles, whilst the firing reliability of MNs dictates the duration and intensity of individual cycles. We therefore propose that our identified effects on swim frequency and intensity are due to a DA-induced reduction in the firing reliability of cINs and MNs. In order to validate the effects of exogenously applied DA and agonists, we also wanted to test whether DA is endogenously released in the spinal cord of *Xenopus* tadpoles. We bath-applied bupropion, a blocker of the DA transporter (DAT), which is known to boost synaptic DA in other preparations. Bupropion (200μM) mimicked the effects of DA and quinpirole, reducing swim episode duration, burst duration and swim frequency. Our results demonstrate that DA is released endogenously onto spinal neurons in *Xenopus* tadpoles during fictive swimming to reduce their firing probability and inhibit network output.

Poster Ref: P2-C-028

Theme: C: Sensory and Motor Systems

Four weeks of musically cued motor training induces structural changes in the arcuate fasciculus.

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Musical cueing has been reported to be effective in movement rehabilitation programmes following stroke, yet to date no studies have investigated the neural basis of this effect. The present study explored whether musically cued motor learning could drive white matter plasticity in the arcuate fasciculus (AF). Differences in Fractional Anisotropy (FA), a biomarker of white matter structure measured using Diffusion Tensor Magnetic Resonance Imaging (DT-MRI), in the AF have previously been found between musicians and non-musicians, interpreted as relating to auditory-motor connectivity. Additionally, differences in FA in the corticospinal tracts (CST), which communicate motor information, have previously been found to predict auditory-motor learning speed.

Thirty healthy, right-handed, non-musician, adult volunteers participated in the study. Participants were assigned to either the Music Group or Non-Music Group, and completed 4-weeks training of a visuo-motor sequencing task using the fingers of the left hand, with or without musical cueing, respectively. Participants underwent DT-MRI scans pre and post-training and completed a fine motor skills assessment pre, mid and post-training. We hypothesised that 1) FA in the right AF would increase following training within the Music Group only and 2) that FA in the right CST would correlate with initial fine motor ability across both groups.

As hypothesised, FA in the right AF significantly increased post-training ($p = 0.035$), with no significant changes observed in the Non-Music Group ($p = 0.288$), or in the left AF of either group. Contrary to our hypothesis, FA in the right CST did not correlate with initial fine motor skill ($R = 0.278$, $R^2 = 0.077$, $p = 0.179$).

For the first time in a longitudinal setting, moving to music has been shown to lead to specific learning-related plastic changes in the brain, which are perhaps indicative of an increase in connectivity between the auditory and motor regions of the brain. Musical cueing should thus be further explored as a tool to stimulate brain plasticity. In particular, evidence of plasticity following movement entrainment to music may have implications for movement rehabilitation following stroke, where structural re-organisation is crucial for functional motor recovery.

Poster Ref: P2-C-029

Theme: C: Sensory and Motor Systems

Cortical dynamics across V1 laminae generate independent frequency channels encoding visual information.

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Previous studies have shown that population level activity in the primary cortex (V1) encodes information about natural stimuli into two distinct frequency regions, one above and one below 40Hz [1]. However, the origins and function of these two frequency bands are as yet unknown.

We investigated the encoding of visual information across the joint domains of frequency and depth within a single cortical column of V1. Using laminar electrodes (150 micron spacing), we recorded broadband local field potentials and spiking activity in 4 anaesthetised macaques during the presentation of a naturalistic movie.

We found information was highest for low frequencies (4-16Hz) in the granular region (layer 4) while for higher frequencies (60-200Hz) at was highest in the supra-granular region (layers 1-3). This suggests the independent channels of information are generated in distinct cortical laminae. Importantly, the distribution of information along cortical depth was different from the distribution of power.

Additionally, we investigated how much information was contained in the neural activity about changes in the stimulus at various spatial frequencies. We found that neural activity in frequency bands below 40Hz contained most information about low spatial frequency components, peaking around 0.2 cycles per degree. Neural oscillations at frequencies above 40Hz contained most information about higher spatial frequencies, peaking around 2 cycles per degrees.

These results shows that 1) visual information in V1 can be decomposed into two broad frequency bands, likely arising through different mechanisms, and 2) the information encoded in these bands is differs in spatial content.

References.

[1] Belitski, A., Gretton, A., Magri, C., Murayama, Y., Montemurro, M. A., Logothetis, N. K., & Panzeri, S. (2008).J Neurosci, 28(22), 5696-5709.

Poster Ref: P2-C-030

Theme: C: Sensory and Motor Systems

Priors for perceptual decision in pre-stimulus phase of occipital alpha-band EEG.

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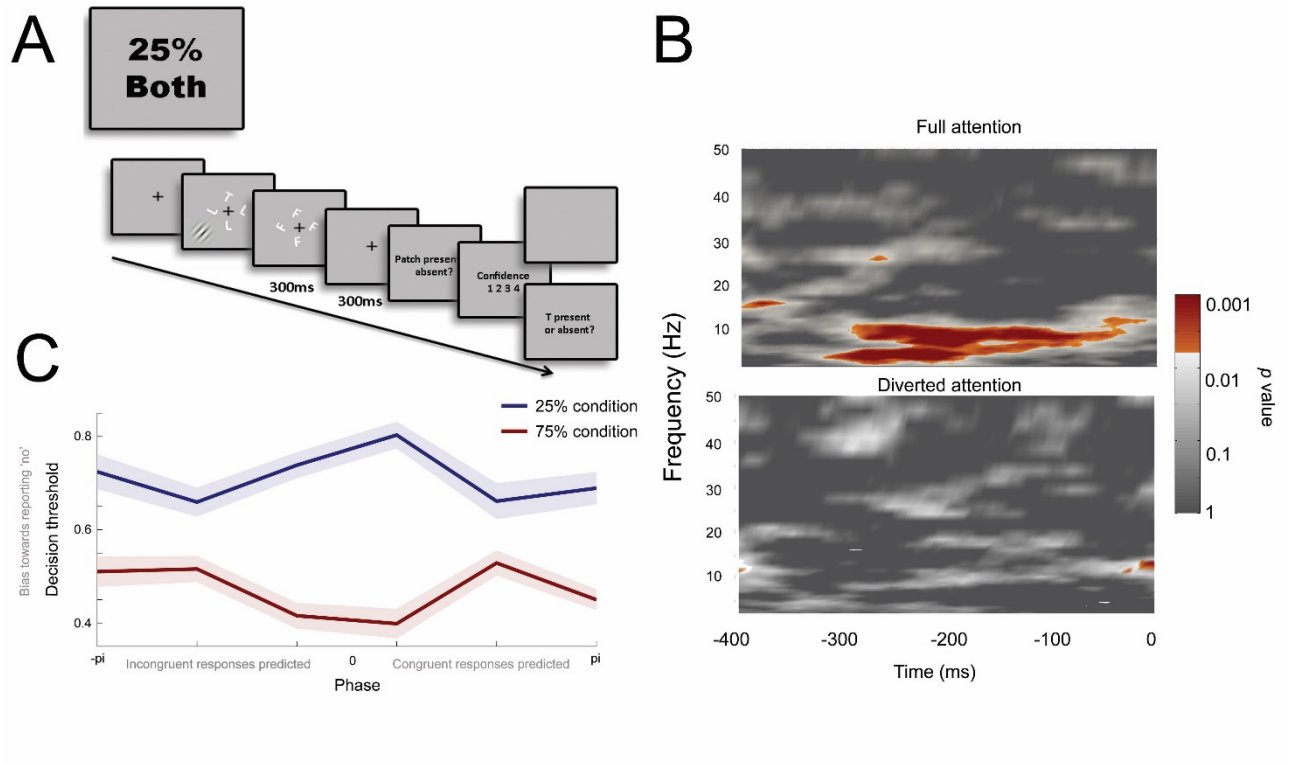
Background: Perception is influenced by both prior expectation and endogenous attention. Recent work suggests that spontaneous alpha oscillations reflect attentional cycles, which periodically modulate sensitivity. However, the mechanism by which priors modulate perception remains unclear. Recent work suggests α/β band oscillations communicate top-down information, while the γ-band communicates bottom-up signals. We therefore asked whether the influence of expectation on decision oscillates with spontaneous α/β phase.

Method: We collected scalp EEG over 18 healthy subjects during a dual-task detection paradigm. Attention and expectation were factorially manipulated. Prior expectation of target absence/presence was induced by changing the frequency with which a to-be-detected Gabor appeared (25/75%). Attention was manipulated by *via* the task-relevance of Gabor detection (ignore/perform concurrent visual search). The visual search array and Gabor were presented simultaneously, allowing time-locking to Gabor presence and absence. We also collected post-decision confidence ratings.

Results: Time-frequency (tf) decomposed pre-stimulus EEG activity over occipital electrodes revealed that ongoing 10Hz phase predicted yes versus no responses only under full attention. Phases at the tf point maximally predictive of choice were binned. This allowed us to compute SDT decision threshold and sensitivity measures as a function of attention, expectation and phase.

Follow-up analyses under decision threshold revealed that expectation-in/congruent decisions were predicted by α phase. This effect was accompanied by conservative shifts in confidence biases. We found no evidence for phase modulation of type 1 d'.

Conclusions: Collectively, our data provide evidence for an ongoing rapid, periodic alternation between top-down and bottom-up influences on decision in visual areas: At the preferred phase for top-down prior influences (0°) decisions are maximally biased by top-down expectation and are maximally underconfident; at the suboptimal phases where bottom-up signals exert greater influence, confidence increases. These data have implications for Bayesian theories of perception by indicating that expectations impose their influence at specific phases of oscillations.



A. Trial sequence for the 25%, divided attention condition B. Time-frequency representation of phase modulation of yes vs. no. Coloured regions have survived fdr correction for multiple comparisons for dependent observations. C. Phase modulation of c1. Positive c1 represents a bias towards reporting 'no' and negative c1, a bias towards reporting 'yes'. Shaded outlines represent within-subject SEM.

Poster Ref: P2-C-031

Theme: C: Sensory and Motor Systems

Developing an automated measure of facial imitation to predict empathic ability.

James Cusack, Isobel Cameron and Justin H G Williams

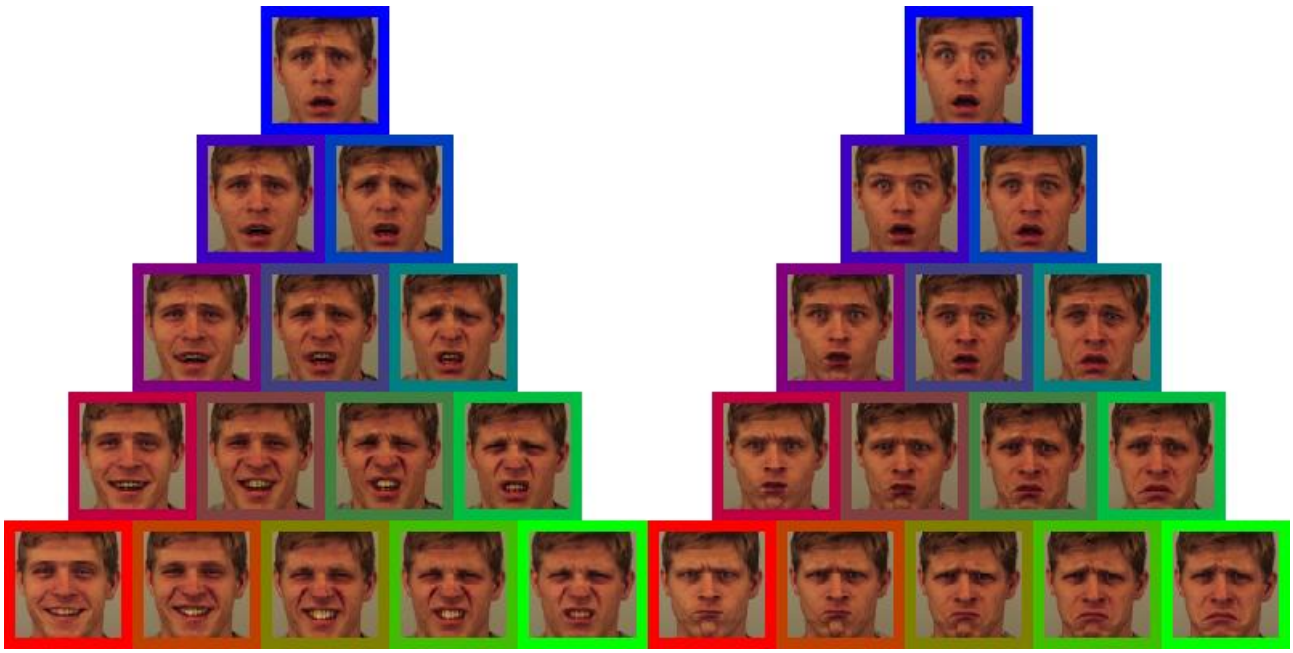
Institute of Medical Science, University of Aberdeen

Rationale: The capacity of humans to understand and respond to the mental states of others is a crucial aspect of human cognition. This capacity has evolved from primates - where understanding of others has been linked to the discovery of mirror neurons. One implication of this research is that the mirror neuron system underpins a common capacity for both imitation and empathy. A recent facial imitation task revealed an association between imitation accuracy and a self-reported measure of empathic traits (the Empathic Quotient – EQ).

Methods: The task indexes facial imitation ability by the degree to which participants can evidence a capacity to discriminate between expressions of varying degrees of similarity in their imitated copies. 19 participants imitated each expression from the stimulus array (fig. 1) of facial expressions twice. A webcam video recorded expression from neutral to expressive. We selected first 3 (neutral) and final 3 (expressive) frames. Face Detection (Viola-Jones) was then applied and a local feature shape model was fitted to intuitive features. We fitted each shape model to an average shape. The median of neutral and expressive features was taken. We then took the difference between expressive and neutral. Symmetric features were then summed and weighted according to their reliability. We were able to calculate what proportion of a given emotion was evident in an emotional expression and how this corresponded to the stimulus quantity. We desynchronised the stimulus quantities to index the participant's discriminant validity – a measure of facial imitation fidelity.

Results: Reliable feature selection was demonstrated - the stimuli model correlated with the average participant ($r(1859)=0859$, $p<0.001$), but was significantly smaller (Fisher's r-to-z: $p<0.001$, $z=26.19$) when the values were desynchronised ($r(1859) =0.4014$, $p<0.001$). The measure was reliable when accuracy between repeat conditions were compared ($r (16) = 0.6335$; $p=0.0084$). Our measure correlated with EQ scores ($r (15) = 0.765$, $p = 0.0009$).

Discussion: Our automated measure of facial imitation fidelity provides an automated quantitative behavioural measure of empathic traits, supporting the view that empathy and imitation are reliant on common underlying cognitive mechanisms.



The stimuli presented is a series of facial expressions constructed by quantitatively morphing 3 stereotypical expressions in varying amounts in 2 separate arrays (happy, fear, disgust; sadness, anger, surprise). This way, 15 expressions are created which vary from one another by different degrees, from being subtly different to markedly different.

Theme D: Learning, Memory and Cognition

Posters P2-D-001 to P2-D-061

Poster Ref: P2-D-001

Theme: D: Learning, Memory and Cognition

Prediction of light-modulated learning from the Cortical Electroencephalogram.

Sibah Hasan, Eric Tam, Russell Foster and Stuart Peirson

University of Oxford

Light exerts a powerful, immediate effect on physiology and behaviour, in addition to its strong influence on circadian organization. In humans, bright light influences body temperature, reduces sleepiness and improves alertness measured by waking electroencephalography (EEG) as well as performance. In nocturnal animals such as rodents, light exposure during the night results in rapid sleep induction, whereas dark exposure during the day results in waking. As such, little is known about how light affects cognitive performance in mice. Here we have assessed the effects of different light intensities (5, 50 and 500 lux) on the waking EEG and cognitive performance, using novel object and odour recognition tasks in adult male mice. The protocol consisted of 6 experimental trials (Object: 1st–3rd trial; Odour: 4th–6th trial), where mice were kept in darkness during the first half of the subjective day (CT0-CT6) before the task at CT6 (middle of the subjective day). Mice exposed to 50 and 5 lux light performed significantly above chance ($P < 0.05$) for both object and odour recognition, but animals exposed to 500 lux did not perform above chance. In the odour modality, mice exposed to 5 lux performed better than with 500 lux (Post-Hoc, $P < 0.05$). Trial performance was then compared against waking EEG spectra. Prior sample theta power (8–11 Hz) during the sample phase was a good predictor of performance during the test phase, where light-modulated sample theta activity was negatively correlated with both object (Pearson Corr. $P < 0.005$) and odour recognition performance ($P < 0.05$). Gamma activity (35–50 Hz) during the test phase was also a good predictor of performance during object (but not odour) memory recall. Gamma activity was positively correlated with object recognition performance ($P < 0.05$). By using light intensity as a stimulus to modulate arousal, we have identified waking EEG correlates of memory performance in mice. This is the first direct evidence that electrophysiological correlates from the cortical EEG in mice provide a predictor of learning and short-term memory performance. This present study also show for the first time an arousal effect of light in a nocturnal species, establishing then a valuable rodent model of alerting effects of light.

Poster Ref: P2-D-002

Theme: D: Learning, Memory and Cognition

Distinct changes in executive control and anaesthetised resting state functional connectivity after damage to the magnocellular mediodorsal thalamus in monkeys.

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The mediodorsal thalamus (MD) and the prefrontal cortex are reciprocally interconnected. However, MD damage in monkeys does not always cause cognitive deficits in tasks shown to be sensitive to prefrontal cortex damage (Mitchell and Gaffan, 2008). Evidence from patients with stroke damage that includes MD suggests that MD has a role in supporting the prefrontal cortex in executive control. This proposal was investigated in monkeys using a computerised version of the Wisconsin Card Sorting task (Mansouri *et al*, 2007; Buckley *et al*, 2009). Monkeys were trained pre-operatively to learn colour and shape matching rules and displayed cognitive flexibility when switching between these matching rules. After selective, circumscribed bilateral neurotoxic lesions to the magnocellular subdivision of MD (MDmc), within subject comparisons of pre-operative verses post-operative performance demonstrated differences in cognitive flexibility. This difference in behavioural performance after MDmc damage was similar to the behavioural changes observed after selective damage to orbital frontal cortex (Buckley *et al*, 2009). Resting state functional magnetic resonance imaging also demonstrated changes in cortical connectivity while monkeys were anaesthetised. This evidence supports proposals that MDmc provides a unique functional role, *via* its interactions with the cortex, for specific aspects of executive control.

Poster Ref: P2-D-003

Theme: D: Learning, Memory and Cognition

Electrophysiological findings of syntactic anomalies in patients with bipolar disorder and schizophrenia: a P600 study.

Sung Hwa Kim[1,2], Chang Woo Lee[1], Vin Ryu[3], Ra Yeon Ha[1], Su Jin Lee[2], Jee Soo You[2] and Hyun Sang Cho[1,2]

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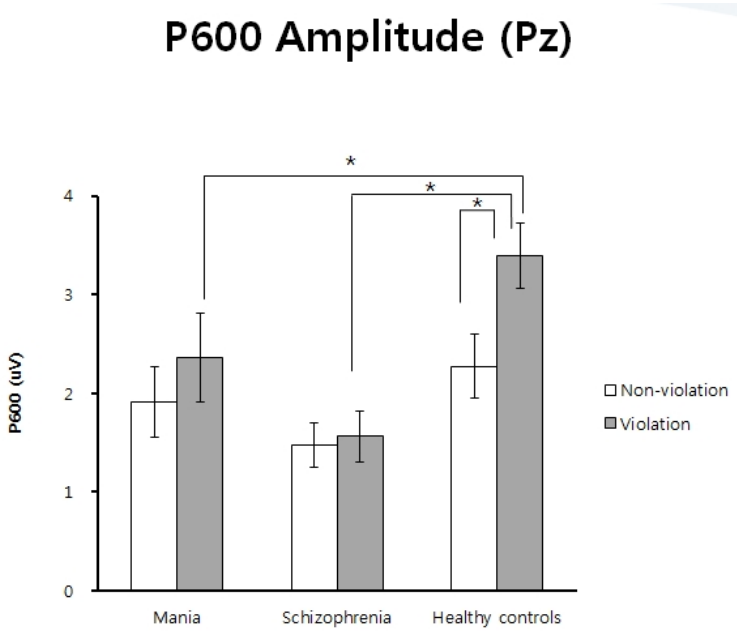
Objectives: Manic patients are known to show the symptoms of abnormal semantic and formal thoughts. The P600 is an event-related potential which is thought to be elicited by syntactical errors in listening and reading condition. We examined the alteration of the P600 wave according to auditory syntactic violation in manic patients with bipolar disorder and schizophrenia compared with healthy controls.

Methods: Twenty-one manic bipolar patients, twenty-six schizophrenia patients, and twenty-nine healthy controls were recruited. We recorded the electroencephalogram during the task employing the auditory syntactic violation sentence paradigm.

Results: P600 amplitude analysis showed the main effect for syntactic violation (Midlines: $F=6.84$, $p=0.011$, Laterals: $F=5.12$, $p=0.027$), for group (Midlines: $F=6.37$, $p<0.003$, Laterals: $F=8.55$, $p<0.001$, and the interaction of violation x group (Midlines: $F=3.20$, $p=0.047$, Laterals: $F=3.60$, $p=0.032$) in both midline (Fz, Cz, Pz) and lateral (F3,C3,P3,F4,C4,P4) sites. The healthy controls showed the increased P600 amplitude like other previous studies. The manic and schizophrenic patients showed significantly decreased P600 amplitude to syntactically violated stimuli in comparison to healthy controls. However, there were no significant differences among the two patient groups.

Conclusion: These results suggest possible electrophysiological evidence for abnormal processing of grammatical and syntactic anomalies in both patients with bipolar disorder and schizophrenia. P600 abnormality is associated with both language-specific deficit of syntactic integration and cognitive deficits. This result might support that bipolar disorder and schizophrenia share common clinical manifestations and cognitive impairment. In the future, we will need the investigation of qualitative difference in language processing between bipolar disorder and schizophrenia.



P600 Amplitudes were recorded at Pz electrode

* p<0.05, Error bars: standard error mean

Poster Ref: P2-D-004

Theme: D: Learning, Memory and Cognition

Differential glucocorticoid dynamics produce altered activation/deactivation maps in the corticolimbic areas of the human brain under emotional stimulation. Preliminary data from a pilot fMRI study.

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[1]University of Bristol, [2]University of Oxford

Background: Glucocorticoids' (GCs) rhythmicity is a dynamic biological factor for their regulatory effects, particularly important in the parts of the brain that show high sensitivity to GCs. Such brain regions, like the corticolimbic structures, are abundant in glucocorticoid- and mineralocorticoid receptors, through which GCs modulate various cognitive and behavioural phenotypes in humans.

Aim: To examine the effect of different temporal patterns of glucocorticoid presentation on emotional processing with the application of functional magnetic resonance imaging (fMRI).

Methods: 6 healthy, male, right-handed individuals participated in an interventional, double-blinded, placebo-controlled, crossover study. The three treatment schemes had a duration of 5 days. All participants received oral metyrapone loading (gradually increasing total daily dose from 0.5g to 2.5g) to suppress endogenous cortisol adrenal activity. A fixed total daily dose of hydrocortisone 20mg was exogenously replaced *via* 3 different methods (1 per treatment arm): (a) orally, (b) subcutaneously in a continuous manner and (c) subcutaneously in a pulsatile manner. Individuals participated in a functional neuroimaging and behavioural study on day 5. As part of that study, participants underwent a facial expression recognition task (FERT) based fMRI session; the controlled block design aimed to stimulate the recruitment of brain regions involved in emotional processing. Functional data were analysed using FSL software (FEAT) at an individual and group level. The mean effect of the task under each of the 3 alternative treatment strategies was estimated in GCs-sensitive areas of the brain (predefined regions of interest).

Results: The extent of corticolimbic areas' participation (as reflected by activation and deactivation maps comparing the BOLD response during the FERT with a baseline -no stimulus- condition) in the cognitive processing of emotional stimuli varies between the 3 groups of alternative patterns of glucocorticoid replacement (results blinded).

Conclusion: These pilot data support the capability of altered GCs temporal dynamics to differentially modulate the level or mode of activation of susceptible brain areas.

Poster Ref: P2-D-005

Theme: D: Learning, Memory and Cognition

The human hippocampus represents the topological structure of the environment during navigation.

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[1]University College London, [2]University of Hertfordshire, [3]University of Bahrain

The rodent hippocampus appears to simulate the structure of the paths in environment during 'off-line' rest states [1, 2]. Such hippocampal representations appear to be fragmented, with entry into each sub-region of an environment requiring activation of a new map [3, 4]. Using functional magnetic resonance imaging, a virtual simulation of London (UK), and graph-theoretic measures of street network connectivity, we examined whether hippocampal activity reflects the topological properties of the streets navigated through. Analysis revealed that, during navigation, right posterior hippocampal activity significantly increased when the new street entered had more streets connected to it than the previous street passed through. In a control task, in which subjects were guided to their goal by external cues, we found no significant modulation of hippocampal activity during such events, and activity was significantly less driven by changes in street connectivity than during navigation. In our experiment we had subjects choose their next street prior to entering it. This allowed us to separate responses during decision-making and subsequent street entry. Much like new street entry, during decision-making we found that right posterior hippocampal activity was higher when the street chosen to enter had more connections than the street currently occupied. These findings are consistent with the hippocampus simulating possible future trajectories when entering a new space and planning to enter a new space.

[1] Wu, X., & Foster, D. J. (2014). Hippocampal Replay Captures the Unique Topological Structure of a Novel Environment. The Journal of Neuroscience, 34(19), 6459-6469.

[2] Jeffery, K., & Casali, G. (2014). Hippocampal Neurons: Simulating the Spatial Structure of a Complex Maze. Current Biology, 24(14), R643-R645.

[3] Derdikman, D., Whitlock, J. R., Tsao, A., Fyhn, M., Hafting, T., Moser, M. B., & Moser, E. I. (2009). Fragmentation of grid cell maps in a multicompartment environment. Nature neuroscience, 12(10), 1325-1332.

[4] Spiers, H. J., Hayman, R. M., Jovalekic, A., Marozzi, E., & Jeffery, K. J. (2013). Place field repetition and purely local remapping in a multicompartment environment. Cerebral Cortex, bht198.

Poster Ref: P2-D-006

Theme: D: Learning, Memory and Cognition

Structural brain changes in obesity and binge-eating disorder.

Tom Mole[1], Elijah Mak[1], Yee Chien[1], Michael Irvine[2], Neil Harrison[3], Trevor Robbins[1] and Valerie Voon[1]

[1]University of Cambridge, [2]University of East Anglia, [3]University of Sussex

Introduction: Neural regions implicated in reward-processing have been shown in some studies to be abnormal in disorders of addiction. However, little is known about how brain structure may differ in obesity (OB) or in obesity with binge-eating disorder (BED). We hypothesised that key regions implicated in reward-processing such as the striatum would be altered in OB and BED.

Methods: 84 subjects in three groups comprising OB (n=20), BED (n=22) and healthy volunteers (HV) (n=42) were scanned using an MPRAGE protocol. We performed unbiased whole-brain voxel-based morphometry analysis using Statistical Parametric Mapping and a confirmatory automated subcortical volume analysis using Freesurfer focusing on a priori regions. Age and total intracranial volume were used as covariates of no interest.

Results: Voxel-based morphometry whole-brain analysis in (OB + BED) vs HV showed increased volumes in the ventral striatum (FWE whole-brain cluster corrected $p<0.05$). Confirmatory automated segmentation of subcortical structures similarly showed increases in striatal volume particularly in the nucleus accumbens area. Conversely, total subcortical grey-matter was reduced in (OB + BED) vs HV. When all three groups were combined, BMI (Body Mass Index) correlated positively with accumbens volumes. In BED alone, putaminal volumes negatively correlated with the Binge Eating Scale score (correlation=-0.569 p=0.021).

Discussion: We show an increase in ventral striatal volume in obesity correlating with BMI. Results were internally validated by independently replicating findings across two independent neuroimaging methods. Our findings suggest a potential role for abnormalities in reward or motivational processes in obesity.

Poster Ref: P2-D-007

Theme: D: Learning, Memory and Cognition

Lateral entorhinal cortex lesions impair object-place recognition in both an egocentric and allocentric task.

Kuruvilla Maneesh, David Wilson and James Ainge

University of St Andrews

There is consistent evidence to demonstrate that hippocampal place cells encode spatial information within familiar environments. However, the role that hippocampal inputs, specifically from the entorhinal cortex, play in this spatial representation is still largely debated. Grid cells within the medial entorhinal cortex (MEC) generate spatial grids that could explain place cell formation. The lateral entorhinal cortex (LEC), on the other hand, is thought to be involved in processing non-spatial, contextual information. Recently, however, some authors have argued that the LEC may represent an egocentric worldview of local cues of an environment within a spatial framework. We tested rats with LEC lesions on an object-place memory task. In the sample phase, rats were allowed to explore an environment containing two different objects. In a test phase rats were allowed to explore two new copies of one of the objects; one in a position in which it had been previously experienced and one in a position in which it had not been experienced. The test phase was run with two variations: rats were either placed in the environment facing the same location every time in order to promote egocentric/local cue processing or they entered the environment from multiple locations to encourage allocentric navigation/global cue processing. Control rats performed both tasks well, spending significantly more time exploring the object in a novel place relative to the object in a familiar place irrespective of start location. LEC lesioned rats, however, performed at chance in the egocentric/local cue version exploring both objects equally but explored the object in the novel location significantly more in the allocentric/global cue version. LEC rats were still impaired relative to shams, however, in the allocentric task. LEC lesioned rats were also tested on a spatial reference memory task on a T-maze. They showed unimpaired performance and were also significantly better than controls on day 1 of testing. The results suggest that rats with LEC lesions are impaired at solving a local cue-dependent task but can use global cues to guide behaviour and remember previously experienced spatial locations.

Poster Ref: P2-D-008

Theme: D: Learning, Memory and Cognition

Novelty and familiarity processing in the perirhinal-hippocampal network.

Magali Sivakumaran and James Ainge

University of St Andrews

The perirhinal cortex (Prh) has been described as the interface between the neural systems that process perceptual and mnemonic information. Lesions studies demonstrate that the Prh is necessary for novel object recognition (NOR). Early studies report an incremental decrease in Prh neuron firing with increased exposure to objects. This has been described as a familiarity response despite the neuronal firing being highest for novelty. Herein lies an assumption that novelty and familiarity processing are interdependent and potentially part of a single recognition process. However, findings in human fMRI literature suggest that novelty and familiarity are dissociable processes. Furthermore, previous studies suggest the Prh is only required for NOR when objects have high visual feature overlap, while others suggest the Prh is processing object presence in the environment regardless of the object's memory status. We used a modified version of the NOR paradigm to assess how the Prh and other medial temporal lobe (MTL) structures processes novelty in conjunction with varying degrees of familiarity. Following four consecutive days of exposure to two household objects, c-fos expression was measured in four groups of rats. Group 1 experienced a consistent object (A) each day combined with a novel object such that on the final day A was highly familiar. The familiarity of the familiar object A on the final day was manipulated in groups 2 and 3 by varying the number of previous exposures to it. Rats in group 4 (control condition) saw the same two objects on each of the 4 days, such that no novel objects were seen on the final day. By measuring final day Fos expression across the 4 groups we were able to examine how the network processes novel objects relative to objects with varying levels of familiarity. Relative familiarity did not affect behavioural novelty preference. c-fos expression in the Prh was not affected by the familiarity of objects. There was also no difference in Prh Fos expression for animals who had been presented with a novel-familiar object pair and those presented with a familiar-familiar object pair. These data suggest that the Prh is processing familiarity rather than novelty. Structural equation modelling of novelty and familiarity processing in the MTL will be discussed.

Poster Ref: P2-D-009

Theme: D: Learning, Memory and Cognition

LEC lesions impair memory for odour-context associations.

Bjorn Persson and James Ainge

University of St Andrews

The use of contextual information has been argued to be important for separating similar events in memory. While it has been demonstrated that both humans and rats are capable of using context to disambiguate events, it is still debated where this contextual information is processed in the brain. Previous research suggests that item-context information is bound in the lateral entorhinal cortex (LEC), which along with the medial entorhinal cortex is one of the main input streams to the hippocampus. The current study builds on this research by testing whether the LEC is involved in multimodal item-context associations, more specifically odour-context associations. Previous research has predominantly used the object recognition paradigm which induces relatively short term memory and so the current study also aimed to examine a longer lasting item-context association. Rats were trained to dig for rewards in pots filled with scented sand in two different contexts. In the first context (checked) a reward could be found in the bowl scented with mint, while if digging in the bowl scented with coriander the rat got no reward. The opposite rule applied to the second context (Christmas) where digging in coriander gave a reward, and mint gave no reward. After reaching a performance level of 75% correct trials over two consecutive days, rats either received bilateral LEC lesions or bilateral sham lesions. The LEC was lesioned using ibotenic acid, while for sham lesions only the vehicle solution (sterile phosphate buffer) was injected in to the LEC. Following surgery rats were tested on the previously learned odour-context associations, as well as on odour and context discriminations in order to rule out any deficits in olfactory or visual processing alone. Results showed a significant decrease in performance between pre- and post-surgery for the LEC lesions group, but not for sham animals on memory for the previously learned odour-context associations. However, there were not differences between the groups in their ability to discriminate between odours or contexts. This indicates that the LEC is involved in the memory for multimodal associative information.

Poster Ref: P2-D-010
Theme: D: Learning, Memory and Cognition

Defining the role of α7 nicotinic acetylcholine receptors in the medial prefrontal cortex.

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University of Bath

The medial prefrontal cortex (mPFC) is a key brain region implicated in numerous neurological disease states including addiction and schizophrenia (1, 2). The mPFC encompasses a variety of neurotransmission systems to regulate activity, one of which being the cholinergic system. Nicotinic acetylcholine receptors (nACHRs) in particular are expressed throughout the mPFC and are able to regulate mPFC activity (3).

Using brain slice electrophysiology in mice, we have shown that α7nAChRs reside both on cell bodies of GABA interneurons and on glutamatergic nerve terminals in the mPFC, enabling bidirectional control of excitability of mPFC pyramidal neurons. Further, tonically released acetylcholine appears to selectively target α7nAChRs located at glutamatergic nerve terminals.

We next tested the hypothesis that not all glutamatergic afferent fibres within the mPFC possess α7nAChRs. To test this we selectively evoked mPFC glutamate from the hippocampus by stimulating a defined glutamatergic tract from the ventral hippocampus (4). Upon sequential bath application of the α7 positive allosteric modulator (PNU-120596), α7 selective agonist (PNU-282987) and the α7 antagonist (MLA) no significant change in the levels of evoked hippocampal glutamate was found, suggesting α7nAChRs may not reside on hippocampal terminals in the mPFC.
Glutamatergic afferents arising from the thalamus largely express μ-opioid receptors allowing us to selectively inhibit thalamic glutamate terminals within the mPFC with the μ-opioid agonist DAMGO (5). DAMGO inhibited the frequency increase of spontaneous excitatory postsynaptic current (sEPSC) seen with application of the α7 PAM PNU-120596 alone. This initial evidence suggests α7nAChRs may reside on thalamic terminals.

Ongoing work utilises optogenetics to selectively activate glutamate from different brain regions, to further elucidate the precise location of α7nAChRs within the mPFC.

(1) Van den Oever MC *et al.* (2010) Neurosci and Biobehav Rev 35: 276-284.
(2) Lewis DA (2009) Dialogues ClinNeurosci 11: 269-280.
(3) Poorthuis RB *et al.* (2012) Cerebral Cortex 23:148–161.
(4) Parent MA *et al.* (2009) Cereb Cortex 20: 393-403.
(5) Lambe EK *et al.* (2003) Neuropsychopharmacology 28: 216-225.

Poster Ref: P2-D-011

Theme: D: Learning, Memory and Cognition

Drift diffusion modelling of rodent behavioural data from a judgement bias task following negative affective state manipulations.

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Background: In humans, judgement bias is one type of cognitive process influenced by emotions. Judgement biases can also be measured in rodents, and can be altered by affective state. However, changes in decision making processes underlying this bias have not been explored. A rodent ambiguous cue interpretation task was used to study judgement bias following negative affective state manipulations. Behavioural data from this task were fit to a drift diffusion model to provide insight into the cognitive processes involved in decision making. We aimed to investigate how negative affective state alters diffusion model parameters of interest.

Methods: Male Lister hooded rats (n=10) were trained to discriminate between two auditory tones and make a response on the appropriate lever to either obtain high or low value reward. Judgement bias was measured following an acute pharmacological and a chronic stress negative affective state manipulation by analysing responding to midpoint ambiguous tones. Changes in diffusion model parameters corresponding to distances to upper and lower boundaries and rate of information accumulation were calculated from behavioural data.

Results: In both experimental manipulations, rats made more responses on the low reward lever to the midpoint tone, indicative of negative judgement bias ($ps \leq 0.041$). Diffusion model analysis showed that for the acute manipulation, this reflected dose dependent increases in distance to boundaries ($ps \leq 0.038$), along with a more negative drift rate ($p=0.001$). Distances to boundaries were also increased for the chronic manipulation ($ps \leq 0.030$). This suggests decision making is more cautious, and judgements are more pessimistic when in a negative affective state.

Conclusions: This study shows that it is useful to combine computational modelling with a rodent behavioural task in order to probe the cognitive processes underlying negative judgement bias. The diffusion model is advantageous as it uses the full temporal profile of behavioural responses. This may be a valuable method to investigate the complex interactions between cognition and emotion, and be particularly beneficial for psychiatric research as negative cognitive biases are known to be involved in the development, maintenance and treatment of mood disorders.

Poster Ref: P2-D-012

Theme: D: Learning, Memory and Cognition

Neural, demographic and lifestyle correlates of aggregate cognitive performance and successful cognitive ageing.

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Although age-related differences in performance in most cognitive domains have been frequently reported, there have only been limited attempts to integrate these differences across domains into a single estimate of cognitive ageing and identify its demographic, lifestyle and neural correlates. In the present study, we characterise cognitive health index (CHI) as the common factor underlying performance across a diverse set of behavioural measures, including reasoning, memory, motor function and language. The basis of our analysis is a large, population-derived sample (N = 452, aged 25-85) from the Cambridge Centre for Ageing and Neuroscience (www.cam-can.org), that allows for testing both age-independent and age-related factors of cognitive health. Validating our approach, we found the obtained CHI to correlate with widely-used medical diagnostic measures of dementia and cognitive impairment (ACER and MMSE). Key demographic, lifestyle and mental health variables, such as education level, reading, smoking, depression and anxiety, were also significantly correlated with CHI across the entire age range. In contrast, a composite measure of social connectedness exhibited increasing correlation with CHI only for participants older than 65, highlighting its importance in successful ageing. Voxel-based morphometry analysis of grey matter volume showed a significant correlation between bilateral frontal regions and CHI. Furthermore, we found that CHI is highly related to integrity of white-matter tracts connecting the frontal lobe to posterior cortical areas (superior longitudinal fasciculus) and to the thalamus (anterior internal capsule). These findings represent a step toward an integrated, multi-level explanation of healthy cognitive functioning and successful cognitive ageing.

Poster Ref: P2-D-013

Theme: D: Learning, Memory and Cognition

Metabolic changes in the retrosplenial cortex following mammillothalamic tract lesions.

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Cardiff University

Lesions within the medial diencephalon lead to a reduction in the expression of immediate-early genes (IEGs) in the superficial granular retrosplenial cortex (RSG). It remains unclear, however, whether these changes contribute to the lesion-induced behavioural deficits. Here, we employed a marker for neuronal metabolic activity, cytochrome oxidase (COX), to further elucidate the lesion-induced pathology of the RSG. We chose to lesion the mammillothalamic tract (MTT) to avoid direct damage to retrosplenial inputs and because MTT lesions produce robust deficits on spatial memory tasks in rats. It was found that lesion-induced memory impairment was accompanied by an increase in the levels of COX in the superficial RSG. This result contrasts with a previous report by Mendez-Lopez, *et al.* (2013) of decreased COX levels after lesioning the anterior thalamic nuclei (ATN). That disruption to the different structures of the medial diencephalon produces similar behavioural deficits yet differential metabolic changes in the retrosplenial cortex highlights how vulnerable to disequilibration this brain structure may be and is consistent with the literature on Alzheimer's patients.

Poster Ref: P2-D-014

Theme: D: Learning, Memory and Cognition

The role of L-type voltage gated calcium channels in associative learning.

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Variation in CACNA1C consistently and robustly shows genome-wide significant association with schizophrenia and other psychiatric illnesses. CACNA1C codes for an L-type voltage-gated calcium channel alpha-1 subunit. Calcium influx through these channels is necessary for certain types of synaptic plasticity and learning. Associative learning deficits are prevalent cognitive impairments seen in schizophrenia. The role of calcium channel signalling pathways in these cognitive processes known to be affected in schizophrenia is not yet fully understood. By investigating the activity-dependent expression profiles of CACNA1C during associative learning and the effects of inhibiting these pathways, we aim to understand the possible molecular mechanisms that link the genetic risk with specific symptoms of psychiatric illnesses.

Following contextual fear conditioning, we found evidence of learning-dependent regulation of expression of CACNA1C, with different profiles observed between regions of interest. The L-type specific inhibitor diltiazem, was found to have a specific effect on consolidation, while having no effect on acquisition or recall when compared to infusions of PBS. There was no effect of diltiazem on extinction training, however diltiazem was found to affect the consolidation of extinction and the effects of latent inhibition when tested 24 hours later.

Our results demonstrate that L-type calcium channel genes play a role in associative and inhibitory learning and that inhibition of these pathways in the hippocampus has a specific effect on the consolidation of associative memory. The disruption of these pathways may provide a molecular link between the identified genetic risk and associative learning deficits observed in schizophrenia and related psychiatric illnesses.

Poster Ref: P2-D-015

Theme: D: Learning, Memory and Cognition

Essential functions of primate frontopolar cortex in cognition.

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University of Oxford

Brodmann's area 10 is one of the largest cytoarchitecturally defined regions in human cerebral cortex occupying the most anterior part of prefrontal cortex (frontopolar cortex, FPC) and is believed to sit atop a prefrontal hierarchy. The crucial contributions that FPC makes to cognition are unknown. Rodents do not possess FPC but primates do and here we report the results of the first study looking at the behavioural effects of circumscribed FPC lesion in non-human primates. FPC lesions selectively impaired rapid one-trial learning about unfamiliar objects and unfamiliar objects-in-scenes and also impaired rapid learning about novel abstract rules. Object recognition memory, shifting between established abstract behavioural rules, and the simultaneous application of two distinct rules were all unaffected by the FPC lesion. The distinctive pattern of impaired and spared performance across these seven behavioural tasks reveals that FPC mediates exploration and rapid learning about the relative value of novel behavioural options, and shows that the crucial contributions made by FPC to cognition differs markedly from those of other primate prefrontal regions.

Poster Ref: P2-D-016

Theme: D: Learning, Memory and Cognition

Divergent actions of a Kv3 positive modulator on gamma frequency oscillations in the mammalian cortex *in vitro* in rodents treated with chronic PCP.

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Cortical neuronal networks produce synchronized gamma frequency oscillations (30-80 Hz) that are critical for processing and integrating cognitive modalities. Kv3-family potassium channels such as Kv3.1 are selectively expressed in PV+ interneurons in the cortex. Kv3 channels allow fast-spiking PV+ interneurons to fire accurately at high frequencies to orchestrate the activity of cortical networks. Previous studies in patients suffering from schizophrenia[1] and putative animals models[2] of the condition demonstrate an inability of cortical networks to generate coherent gamma frequency oscillations. In addition, post-mortem studies using cortical tissue obtained from patients with schizophrenia report reductions in PV and in the expression of Kv3.1 channels in the remaining PV+ interneurons.

Given that the pharmacological manipulation of PV+ interneurons is a tangible therapeutic target for schizophrenia, we have examined the effect of a novel class of agents that positively modulate Kv3 channels in rodents treated with chronic PCP. Rodent brain slices containing the medial prefrontal cortex (mPFC) were prepared as previously detailed. Persistent gamma oscillations were generated in the prelimbic subregions of the mPFC. In vehicle (saline) animals, application of AUT6 (20μM) caused a significant decrease in the area power from 1.7±1.0 in control to 0.95±0.61 μV^2 in the presence of AUT6; $p < 0.05$, n=11) and peak power (ctrl = 162±142 μV^2 v. AUT6 = 100±88 μV^2, $p < 0.05$, n = 11) of persistent slow (30–50Hz) gamma activity. In contrast, in animals treated with chronic PCP, gamma oscillations were significantly increased for both area power (ctrl = 2.1±0.9 μV^2 v. AUT6 = 3.9±1.8 μV^2; $p < 0.05$, n = 12) and peak power (ctrl = 95.6±47 μV^2 v. AUT6 = 292±223 μV^2; $p < 0.05$, n=12). Furthermore chronic PCP treated animals showed a significant deficit in the novel object recognition test (NOR).

Our results suggest that modulation of Kv3 channels by these novel compounds can improve gamma oscillations in rats treated with chronic PCP. This may mean that modulation of Kv3 channels with these compounds may have the potential to correct disruptions in neuronal synchronization in patients with schizophrenia.

1. Uhlhaas PJ *et al.*, J Neurosci. 2006 26(31):8168-75.
2. Cunningham MO *et al.*, J Neurosci. 2006 26(10):2767-73.
3. Cunningham MO *et al.*, Proc Natl Acad Sci USA 2004 101(18):7152-7.

Poster Ref: P2-D-017

Theme: D: Learning, Memory and Cognition

Target selectivity of the septal GABAergic input in the hippocampus and extra-hippocampal cortical areas of mice.

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University of Oxford

The septo-hippocampal GABAergic pathway has been shown to target selectively GABAergic interneurons of the rat and monkey hippocampus contributing to coordination of activity, such as the generation of theta oscillation. However, the target selectivity of this projection is controversial in the mouse. Using tract-tracing methods, CLARITY, immunohistochemistry and electron microscopy, we have explored the cortical areas innervated by septal GABAergic projections and identified some of the target cells in the mouse.

Retrograde tracer (retrobeads; Lumafluor, USA) injections into the dorsal CA1, CA3 and medial entorhinal cortex revealed non-cholinergic projections from the medial septum (MS). About 2/3 of the labelled cells were ChAT-immunonegative, the largest subgroup being the parvalbumin (PV)-immunopositive neurons (12%, n = 7 animals). Injection of the anterograde tracer PHAL into the medial septum revealed extensive GABAergic projections to the hippocampus, subiculum, presubiculum, parasubiculum, retrosplenial and entorhinal cortices. These same areas were also innervated by PV-expressing MS projections, visualised by Cre-dependent virus pAAV2-EF1a-DIO-EYFP in 6 PV-Cre heterozygous mice.

VGAT-immunopositive GABAergic axons possessing large boutons and non-GABAergic, mostly cholinergic, axons with much finer varicosities could be differentiated. We have tested the immunohistochemical profiles of target cells in the aforementioned cortices for parvalbumin, calbindin (CB), calretinin and NECAB1. Most target somata were immunopositive for at least one interneuron molecular marker in each region. Furthermore, we have tested the target cells of MS GABAergic boutons in the medial entorhinal cortex for the entorhinal principal cell markers reelin and Wfs1. Neither the Wfs1/CB-immunopositive pyramidal cells nor the reelin-immunopositive stellate cells were found to receive septal GABAergic input in layer II. The results suggest that the GABAergic input to the hippocampus and extra-hippocampal temporal lobe areas from medial septum mainly, if not exclusively, targets GABAergic neurons in the mouse.

Poster Ref: P2-D-018

Theme: D: Learning, Memory and Cognition

Disruption of relative reward value by reversible disconnection of orbitofrontal and rhinal cortex using DREADDs in rhesus monkeys.

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Rhinal cortex (Rh) is essential to stimulus-reward association learning in monkeys. Orbitofrontal cortex (OFC) is essential to relative value judgments. Thus disrupting the connections between Rh and OFC ought to produce a performance impairment in a task that requires both stimulus-reward association and comparisons between relative values.

Two monkeys received unilateral Rh aspiration lesions. They were then trained to perform a visually-cued reward size task. At the beginning of each trial, a visual cue signaled the amount of reward (1, 2, 4 or 8 drops – picked at random) available for correctly detecting when a red visual target turned green. The error rates of the monkeys decreased with increasing drop size, and were indistinguishable from unoperated controls. The operant demands were trial invariant, so we interpret the differences in performance across reward size as reflecting the subjective valuation of the expected reward by the monkey as signalled by the cue.

The OFC contralateral to the hemisphere with the Rh removal was injected with a modified lentiviral vector expressing a Gi-coupled receptor, hM4Di, (DREADD – Designer Receptor Exclusively Activated by Designer Drug) that, when activated by systemically delivered clozapine-N-oxide (CNO), causes neuronal silencing. If effective, activation with CNO should lead to a functional disconnection of Rh from OFC. PET studies were used to determine the concentration of CNO required to produce maximal receptor occupancy.

In behavioural testing sessions begun with systemic injection of CNO there was a marked reduction in the discrimination between expected reward sizes, and an overall reduction in error rate for both monkeys. These results, after reversible cortical deactivation provided by the CNO-DREADD system, demonstrate the necessity of the functional connection between OFC and Rh in stimulus-reward coding and relative reward evaluation.

Poster Ref: P2-D-019

Theme: D: Learning, Memory and Cognition

Postmortem analyses of the Lothian Birth Cohort 1936 using array tomography and electron microscopy.

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Age-related cognitive decline places significant financial and emotional strain on older people, their families and society as a whole. Understanding the decline in brain function is critical for the development of novel therapeutics to prolong cognitive health into old age and to gain insight into pathological cognitive aging such as Alzheimer's disease. The Lothian Birth Cohort of 1936 (LBC1936) is a rare group of 1091 individuals for whom there are childhood cognitive test scores, longitudinal cognitive data from age 70, detailed structural brain MRI, genome-wide genotyping, longitudinal epigenetics and a multitude of other biological and epidemiological data. *In vivo* studies of this cohort have already revealed some determinants of lifetime cognitive changes and changes observed within older age. Synapses have been implicated as indicators of cognitive health in the human brain; however, until recently, it was difficult to perform detailed analyses of synaptic structure and protein composition in humans. We have adapted a novel method of tissue preparation at autopsy to allow the study of human synapses in unprecedented detail, using the high-resolution imaging techniques array tomography and electron microscopy. Here we present data from the first donated LBC1936 brain and describe the detailed multi-disciplinary postmortem studies to be used for the remaining cohort. Ultimately, 38 brain regions will be processed for multiple techniques (biochemistry, histopathology, EM and array tomography) providing a wealth of information on brain health and pathology. Our data shows that compared to an Alzheimer's disease patient, the cognitively normal LBC1936 participant (who lived until the age of 77) has a remarkable degree of preservation of synaptic structure. However, signs of degeneration in areas of the brain implicated in cognition (prefrontal cortex, anterior cingulate cortex, and superior temporal gyrus) are observed. In summary, this approach for studying the well-characterised LBC1936 cohort, extends the phenotyping from cognition and brain imaging to the level of single synapses. This will allow unprecedented study of synaptic integrity during ageing and how it contributes to cognitive change.

Poster Ref: P2-D-020

Theme: D: Learning, Memory and Cognition

Information processing in temporal lobe area TE and in rhinal cortex during a visual categorization task.

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Single unit recordings in regions of inferior temporal cortex - area TE and rhinal cortex (Rh), have implicated these regions in late-stage visual processes, such as categorization and stimulus-reward association, respectively. We have previously reported (SFN, 2012) that TE-lesioned monkeys are only mildly impaired in a perceptually difficult test of visual categorization (employing dog-cat morphs), and that the performance of Rh-lesioned monkeys is indistinguishable from that of controls. Now, we asked whether decreasing the information available by shortening the stimulus duration would affect any of our study groups: controls, or monkeys with either TE or rhinal removals.

We trained the monkeys to touch a bar to initiate a trial, and release the bar during one of two intervals; early (during the presence of a red central target) if they identified the stimulus as more cat-like, or late (following the transition of the central target to green) if the stimulus was more dog-like. A correct response resulted in the delivery of a fixed-size liquid reward, an incorrect response led to a punishment time-out. We presented the morphed stimuli for durations of 25, 50, 100, 250 or 500 ms in an interleaved design. The stimuli appeared on a background of black and white noise. When the stimuli were removed, the background immediately reappeared; the reappearance of the visual noise appeared to mask the after-image.

The accuracy with which control monkeys categorized the stimuli decreased as the stimulus presentation became shorter. The reaction times of control monkeys were indistinguishable across the different stimulus durations.

Bilateral TE and Rh cortex removals had different effects: TE-lesioned monkeys made more incorrect categorization judgments, but made their decisions as quickly as controls. Rh-lesioned monkeys categorized as accurately as controls, but took longer to responds, that is, their reaction times were longer. Thus, TE-lesioned monkeys maintain speed and lose accuracy, whereas Rh-lesioned monkeys give up speed and maintain accuracy.

Poster Ref: P2-D-021

Theme: D: Learning, Memory and Cognition

Implicit visual statistical learning and perceptual inference in chronic schizophrenia.

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Introduction: Patients with schizophrenia have been shown to be impaired in statistical learning and probabilistic inference. Moreover, recent models of schizophrenia suggest that positive-symptoms might stem from learning deficiencies resulting in distorted internal statistical models of the world.

Aims & Methods: We used a recently developed visual statistical learning task known to induce rapid implicit learning of the stimulus statistics. In this task, participants are presented with low contrast visual motion stimuli and need to report the presented direction of motion (estimation task) and whether a stimulus was present or not (detection task). Particular motion directions occur more frequently than others. In controls the implicit acquisition of the statistics of the motion stimuli influences their perception in two ways: 1- motion directions are perceived as being more similar to the most frequently presented directions than they really are (estimation biases); 2- In absence of stimuli, participants sometimes report perceiving the most frequently presented directions (a form of hallucinations). Such behaviour is consistent with the participants using probabilistic inference and combining learnt perceptual priors with sensory evidence. We investigated whether patients with chronic schizophrenia (n=11) differ from controls (n=10) in the acquisition of the perceptual priors and/or their influence on perception.

Results: We found that, although patients were slower than controls, they showed comparable acquisition of perceptual priors, correctly approximating the stimulus statistics. This suggests that patients have no statistical learning deficits in our task. Intriguingly, however, patients made significantly fewer ‘hallucinations’ of the most frequently presented directions than controls ($p=0.0174$, Monte Carlo permutations) and this effect correlated negatively with symptom severity (PANSS Total – $p<0.035$; and PANSS Positive – $p<0.007$; Monte Carlo permutations).

Conclusions: This suggests that perceptual inference differences in chronic schizophrenia appear not to stem from a deficit in implicit visual statistical learning.

Poster Ref: P2-D-022

Theme: D: Learning, Memory and Cognition

Episodic memory in tasks that differ on the basis of place cell response to context.

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Spontaneous Object Recognition tasks, a popular method of studying memory function in rodents, capitalise on rats' propensity to explore novel objects. Variations of these tasks have been found to be reliant on different neural systems. Episodic memory in humans is our memory for events in the past; in rodents, episodic memory is thought to be an integrated representation of components in the environment which make up an event including the memory for What (object) – Where (location) – Which occasion (context) (WWWhich)(Eacott & Norman, 2004). However, a recent publication (Spiers, *et al.*, 2013) found that whilst place fields remapped when well-habituated rats were presented with a different visual context, the same cells failed to re-map to contextually identical chambers in the absence of external visual cues.

Presently, rats were given the WWWhich task under two conditions: one where context was defined in a way that mirrored conditions in which place cells do remap (contextually rich), and in a condition where place cells do not remap (identical contexts). Comparing performance on these two versions of the episodic WWWhich task allows us to understand the way in which behaviour on an episodic memory task is reliant upon remapping to context by place cells in the hippocampus.

Eacott MJ, Norman G. Integrated memory for object, place, and context in rats: a possible model of episodic-like memory? The Journal of Neuroscience. 2004;24:1948-53.

Spiers HJ, Hayman RM, Jovalekic A, Marozzi E, Jeffery KJ. Place Field Repetition and Purely Local Remapping in a Multicompartment Environment. Cereb Cortex. 2013.

Poster Ref: P2-D-023

Theme: D: Learning, Memory and Cognition

A7 nicotinic receptor antagonism selectively reduces reinstatement to morphine-conditioned place preference and significantly reduces morphine induced increases in [^{3}H]AMPA binding in the hippocampus.

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The main challenge in treating drug addiction is maintaining long-term abstinence and preventing relapse after re-exposure to drug associated cues. Nicotinic acetylcholine receptors (nAChRs) were first thought to be involved in the response to nicotine but new compelling evidence suggests they may be involved in the responses to other drugs of abuse (Feng et al (2011) Behav Brain Res 220:100-5) The aim of this work was to characterise the role of α7 nAChRs in morphine reward learning, using conditioned place preference (CPP). Methyllycaconitine (MLA), an α7 antagonist, was used to explore the role of these receptors on different stages of drug-paired learning including acquisition, reconsolidation and reinstatement of morphine-CPP.

7-8 week old C57BL/6J mice were trained in an unbiased CPP protocol in three experiments. 1. Acquisition: animals received either MLA (4mg/kg, s.c) or saline (10ml/kg) 20 mins prior to morphine (10mg/kg, i.p,) or saline conditioning dose. 2. Reconsolidation: 5 days after morphine conditioning, animals were allocated one of two groups, both received one further conditioning trial (morphine) and immediately after received either MLA or saline, followed by a CPP trial 1 day later. 3. Reinstatement: all animals were conditioned to morphine then CPP was extinguished by repeated saline injections. Twenty mins prior to morphine reinstatement (5mg/kg, i.p.) animals received either saline or MLA. Time spent in drug-paired environment (15 min) was measured. Data were analysed using In-vivo stat with a two-way repeated measures mixed model ANOVA and adjusted with Bonferroni's correction for multiple comparisons. Immediately after the behavioural experiments brains were removed for glutamate receptor autoradiography using [^{3}H]AMPA.

MLA significantly inhibited reinstatement, but had no effect on acquisition or reconsolidation of morphine-CPP. In correlation, the autoradiography showed that morphine-primed reinstatement increased, while MLA pretreatment significantly reduced [^{3}H]AMPA binding in CA1 and CA2 of the hippocampus. The findings suggest that α7 nAChRs selectively control drug-primed CPP. With future work we hope to confirm the involvement of the hippocampus in this behaviour by delivering the drug directly into the discrete brain region.

Poster Ref: P2-D-024

Theme: D: Learning, Memory and Cognition

Controlled attentional suppression.

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University of Leicester

When participants are given a cue about the color of distractors in an upcoming array, they are faster to find a target then when no distractor cue is given (Arita, Carlisle, & Woodman, 2012). While the benefit of this cue is not as large as the benefit for a cue that indicates the color of the target, it indicates participants can engage in active suppression of a specific color features. However, other evidence suggests that participants may first need to attend to the distractor color in order to suppress it, a 'search and destroy' mechanism (Moher & Egeth, 2012). In this study, we used the N2pc ERP component to evaluate the conflicting proposals from these two explanations. We used an array that contained 6 items of one color in the left visual hemifield, and 6 items of another color in the right visual hemifield. Participants were provided with a neutral cue (color will not appear in array), a negative cue (color will be distractor), or a positive cue (color will be target). The active suppression hypothesis predicts the cued distractors will be avoided in the negative cue condition, leading to an N2pc toward target features. The search and destroy hypothesis predicts the cued distractors will first be attended, leading to an N2pc toward the cued distractors. We found no evidence of an N2pc toward the cued distractors, in contrast to the prediction of the search and destroy hypothesis. Both the positive and negative cues led to N2pcs toward the target color. The latency of the N2pc response was much faster for the positive cue condition, leading to an interaction of early vs. late window and cue type. Overall, these results show that in some conditions participants can actively avoid a cued distractor feature, suggesting the possibility of active attentional suppression.

Poster Ref: P2-D-025

Theme: D: Learning, Memory and Cognition

Diluted connectivity in pattern association networks facilitates the recall of information from the hippocampus to the neocortex.

Edmund Rolls

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Rolls' theory of the hippocampus (Kesner and Rolls 2014) is different from some other approaches, in that it is a theory of how the hippocampus is involved in memory, and shows how spatial view cells are involved in human episodic memory in which the locations of people or objects in space are stored, and recalled. The recall of information stored in the hippocampus involves a series of cortico-cortical backprojections *via* the entorhinal cortex, parahippocampal gyrus, and one or more neocortical stages. Each stage is considered to be a pattern association network, with the retrieval cue at each stage the firing of neurons in the previous cortical stage. The leading factor that determines the capacity of this multistage pattern association backprojection pathway is the number of connections onto any one neuron, which provides a quantitative basis for why there are as many backprojections between adjacent stages in the hierarchy as forward projections. The issue arises of why this multistage backprojection system uses diluted connectivity. It is shown here that diluted connectivity in the backprojection pathways reduces the probability of more than one connection onto a receiving neuron in the backprojecting pathways, which otherwise reduces the capacity of the system, that is the number of memories that can be recalled from the hippocampus to the neocortex. For similar reasons diluted connectivity is advantageous in pattern association networks in other brain systems such as the orbitofrontal cortex and amygdala; for related reasons in autoassociation networks in for example hippocampal CA3 and the neocortex; and for the different reason that diluted connectivity facilitates the operation of competitive networks in forward-connected cortical systems. This leads to a principle of cortical function: diluted connectivity has the advantage that it does not reduce the memory storage capacity of cortical networks that would occur if there were on average one connection between every pair of randomly connected neurons, which would results in many multiple connections between pairs of neurons.

Kesner,R.P. and Rolls,E.T. (2014) A computational theory of hippocampal function, and tests of the theory: new developments. Neuroscience and Biobehavioral Revieews 48: 92-147.

Poster Ref: P2-D-026

Theme: D: Learning, Memory and Cognition

A GSK-3 inhibitor blocks the induction of LTD in the hippocampus *in vivo* and enhances the accuracy of spatial memory.

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Dysregulation of glycogen synthase kinase-3 (GSK-3) is implicated in various psychiatric and neurodegenerative disorders. However it physiological roles in the CNS are poorly understood. Previously we reported that GSK-3 activity is required for long-term depression (LTD) induced by the synaptic activation of N-methyl-D-aspartate receptors (NMDARs) in the CA1 region of rat hippocampal slices. Here, using *in vivo* recordings we show that a potent GSK-3 inhibitor, CT99021, reversibly blocks the induction of NMDA receptor-dependent form of LTD at CA1 synapses of adult mice. In addition, using behavioural tests, we also found that CT99021 facilitates learning and memory in the Morris water maze. However hippocampus dependent fear memory and behavioural flexibility remained unaffected. These data suggest that a GSK3 dependent process, potentially NMDAR-LTD, may act as an impediment for spatial learning and memory accuracy.

Poster Ref: P2-D-027

Theme: D: Learning, Memory and Cognition

Do lateral mammillary body 'head direction' lesions impair navigation?

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Salient landmarks exert stimulus control over neural representations of location and direction, in the spatial firing of place cells, head direction cells and grid cells. However, it is unclear how these spatially-tuned neurones contribute to landmark-based navigation. To address this question we lesioned the lateral mammillary bodies, an essential node in the head direction circuit, and examined subsequent spatial behaviour on a novel spatial task and a traditional water maze task.

Rats were trained to find a hidden reward in a large, cylindrical environment. This cylinder had high walls and contained 16 sand-filled cups spaced evenly along the floor perimeter. A single landmark, an LED light strip, served as a polarising cue in the environment, and the spatial relationship between the landmark and the reward cup was constant across training. Rats were placed in this environment for 10 trials a day until they chose the correct cup reliably. Probe trials in which the landmark was rotated to a new position in the absence of the rat confirmed that the landmark exerted stimulus control over the digging response.

Rats were then given lesions of the lateral mammillary nuclei (LMN) with ibotenic acid (n=6) or sham lesions (n=6), and re-tested on the same task. LMN-lesioned rats did not differ from sham animals in the average number of errors, rewarded trials, or the percentage of first time correct digs. LMN-lesioned rats also learned a new cup location as quickly as sham-lesioned animals. These results suggest that head direction is not essential for visual landmark control of spatial behaviour, at least in a familiar environment. The rats were then tested in a reference memory water-maze task, and here the LMN rats showed a mild impairment in locating a fixed platform location compared with the sham-lesioned animals. During subsequent reversal sessions, the lesioned rats showed a much more severe deficit, a finding that was replicated in a second water-maze. This suggests that the lateral mammillary nuclei may be essential for learning to navigate in a new environment.

Poster Ref: P2-D-028

Theme: D: Learning, Memory and Cognition

A longitudinal study of cognitive and hippocampal ageing in late life.

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Larger hippocampal size is associated with better fluid intelligence in the elderly, and a reduction in size is associated with cognitive decline and dementia. Our purpose is to test the sensitivity of different hippocampal measurements (manual and automatic) and their relation with cognitive decline in normal elderly people.

The participants (148, 80 men) belonging to Aberdeen 1936 Birth Cohort were investigated twice at ages 68 and 73. All participants took a battery of cognitive tests at both ages as follows: Mini Mental State Examination (MMSE) a screening test for dementia; Raven's Standard progressive Matrices (RPM) measuring nonverbal reasoning; Digit Symbol Score (DS) evaluating the speed of information processing; Auditory Verbal Learning Test (AVLT) assessing memory and learning; Block Design (BLK) tests visuospatial skills; and Uses of Common Objects (UFO), a measure of executive function.

Brain MR images at 1.5 Tesla were acquired at both ages with a T1 SPGR (T1W) MR sequence: 20 ms repetition time, 6 ms echo time, 35° flip angle (α), number of slices 100 to 124, effective slice thickness 1.6 mm and matrix 256×256 with in-plane resolution 1 mm×1 mm.

Hippocampal rounding measurements and Scheltens' hippocampal atrophy scoring were performed from coronal oblique images, manually reconstructed using GE Advantage Workstation 4.3 Volume Viewer. Extraction of hippocampal volume and mask were done automatically in FreeSurfer using the longitudinal processing stream.

The main findings are the positive correlation between 1) the reduction of hippocampal surface and the decline of MMSE, AVLT and BLK (Pearson R=0.239-0.294, p=0.001-0.009); 2) the atrophy of hippocampus (volume) and the same cognitive tests (Pearson R=0.236-0.321, p<0.001-0.007); 3) the negative correlation between Scheltens' score and MMSE (Pearson R=-0.228, p=009).

We conclude that the decline of memory and reduced visuospatial skills are associated with the hippocampal atrophy. The measurements of surface and volume give us a better indication of hippocampal atrophy in relation with the cognitive decline than the rounding measurements and Scheltens' score.

Poster Ref: P2-D-029

Theme: D: Learning, Memory and Cognition

Interventions for preventing and ameliorating cognitive deficits in adults treated with cranial irradiation.

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Background: Cognitive deficits are a common late effect of cranial irradiation given to treat brain tumours or as a prophylactic treatment to prevent cerebral spread. These problems have a serious impact on daily functioning and quality of life. The benefit of pharmacological and non-pharmacological treatment of cognitive deficits in this population is unclear.

Objectives: To perform a Cochrane systematic review to assess the effectiveness of interventions for preventing or ameliorating cognitive deficits in adult patients treated with cranial irradiation.

Methods: In August 2014 we searched EMBASE, MEDLINE, PsycINFO and the Cochrane Register of Controlled Trials for any randomised controlled trials which evaluated pharmacological or non-pharmacological interventions in cranial irradiated adults, with objective cognitive functioning as a primary or secondary outcome. Two review authors independently extracted data from selected studies and performed a risk of bias assessment.

Results: Six studies were included in the review; three studies investigated prevention; three studies investigated amelioration. Due to heterogeneity, a meta-analysis was not possible. Pharmacological intervention studies investigating prevention included memantine compared with placebo, and d-threo-methylphenidate HCl compared with placebo. One non-pharmacological prevention study investigated a rehabilitation program. Pharmacological intervention studies investigating amelioration included methylphenidate compared to modafinil, two different doses of modafinil, and donepezil compared to placebo. No non-pharmacological studies investigating amelioration were eligible. Evidence supported the role of memantine in the prevention, and donepezil in the amelioration, of cognitive deficits. There were a number of limitations across studies, largely due to attrition, but most without high risks of bias. Patient withdrawal affected the statistical power of both studies.

Conclusion: There is supportive evidence that memantine and donepezil may improve cognition, but trials in this condition in future must be powered for at least a 50% dropout in order to minimise the effects of withdrawal of consent and expected mortality and reduce need for imputation procedures. The side effects of treatment are infrequent.

Poster Ref: P2-D-030

Theme: D: Learning, Memory and Cognition

Interoception modulates fear breakthrough in binocular rivalry.

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Interoception is the body-to-brain axis of sensation concerning the state of the internal body and its visceral organs, including the heart. We present a binocular rivalry paradigm in which stimulus presentation is locked to specific phases of the cardiac cycle, to determine the impact of internal cardiac signalling and interoceptive awareness on the perception of ambiguous emotional stimuli. Participants (n = 33) were presented with luminance matched fearful and neutral faces, through dichoptic viewing apparatus. Fear faces were initially degraded to 10% contrast, and then modulated using a 1 down/1 up staircase over 20 reversals, to determine a stable contrast at which the fear face was perceived in a minority of trials. Two interleaved and independent staircases were run with stimulus presentation locked to 1) cardiac systole, 2) cardiac diastole. Results show a significant interaction between cardiac phase and interoceptive accuracy in the detection of fear faces, such that those with high interoceptive accuracy had a reduced breakthrough contrast at systole (M = 19%) compared to those with low interoceptive accuracy (M = 26%) ($F(1, 27) = 4.27$, $p = .048$). Furthermore, metacognitive insight into interoceptive ability (*i.e.* interoceptive awareness) significantly predicted breakthrough contrast of fear faces across both systole and diastole. Heightened sensitivity to fear at systole, as a function of interoceptive accuracy, extends recent demonstrations of an up regulation of fear processing at cardiac systole, by demonstrating a perceptual dominance of fear stimuli at systole in individuals who are objectively good at detecting their own heartbeat. In contrast, the relationship between interoceptive awareness and fear breakthrough suggests that agreement between objective and subjective interoceptive abilities leads to enhanced sensitivity to fear stimuli irrespective of cardiac modulation. Together these results support the role of interoceptive dimensions in shaping emotional responses, and that the detection of fearful stimuli is enhanced in individuals who are more attuned to bodily responses.

Poster Ref: P2-D-031

Theme: D: Learning, Memory and Cognition

Is a mother's dementia a predictor for late-life dementia in her offspring? A brain MRI study in the Aberdeen 1936 Birth Cohort.

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The risk of developing dementia may be influenced by early life factors including maternal environment and inherited genotype. There is evidence that maternal transmission of dementia is a significant risk factor for late life dementia1. Here we examine MRI quantified hippocampal size and atrophy and dementia outcome, in a cohort with detailed information of maternal dementia diagnoses.

A sample of the Aberdeen 1936 Birth Cohort (ABC36) was recruited aged 68y. Maternal dementia was determined by interview. Controls were defined as the offspring of dementia-free mothers confirmed to have lived to 68y. Probands were those with mothers diagnosed with dementia. T1 MRI brain images were obtained at 68y (n=230) and 73y (n=149). Total hippocampal and intracranial volumes were obtained using Freesurfer software. Volume and atrophy were calculated. Dementia outcomes of the sample by 78y were determined by interview, medical records and personal communication.

Of a cohort of 503, 301 members of ABC36 were designated controls and 67 participants were designated probands. 9/301 (3.0%) of controls and 6/67 probands (9.0%) developed dementia by age 78y. Logistic regression found that proband dementia prevalence was significantly greater than control.

Hippocampal volume normalised for intracranial volume did not differ between controls (mean=0.54%, SD=0.05%, n=144) and probands (mean =0.55%, SD=0.05%, n=30) at age 68y (t(172)-0.712, p=0.878) or age 73y (control mean=0.52%, SD=0.06%, n=98; proband mean=0.50%, SD=0.08%, n=18) conditions t(114)=1.07, p = 0.11. Total hippocampal atrophy in the probands was significantly greater (mean=7.0%, SD=7%, n=17) than controls (mean=3.9%, SD=4.2%, n=97).

Here we examine the importance of maternal dementia, as a risk for dementia or Alzheimer's brain pathology. It is striking that the offspring of mothers who developed dementia were almost twice as likely as controls to develop dementia by age 78. Furthermore, hippocampal atrophy in this 'at risk' group is significantly greater than controls at age 68y, possibly preclinical evidence of early Alzheimer's pathology.

Our findings support the hypothesis that maternal dementia is a risk factor for late-onset dementia.

1. Honea RA, Vidoni ED, *et al.* J Alzheimers Dis. 2012;31(3):659-668.

Poster Ref: P2-D-032

Theme: D: Learning, Memory and Cognition

Homeostatic intrinsic plasticity, neural heterogeneity and memory maintenance.

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Neural firing rates must be maintained within a stable range in the face of ongoing fluctuations in synaptic activity. This can be achieved through homeostatic intrinsic plasticity. However, here we show that such a mechanism, while successfully regulating neural firing rates, has an adverse effect on a network's ability to encode and retain memories. This is due to its interactions with Hebbian plasticity; neurons whose firing rates change following potentiation or depression of synaptic inputs will experience modifications in intrinsic excitability toward their homeostatic target, which can cause subsequent synaptic weight variations and disrupt learning. Essentially, this failure is a direct consequence of homeostasis preventing neural heterogeneity to maintain stable activity.

We propose a new mechanism, diffusive homeostasis, in which neural excitability is modulated by a diffuse messenger, specifically nitric oxide, which is known to freely cross cell membranes and homeostatically regulate neural excitability. Information about a neuron's firing rate can be carried by nitric oxide, meaning that an individual neuron's excitability is affected by neighbouring neurons' firing rates as well as its own. We find that this allows a neuron to deviate from the target population activity, as its neighbours will counteract this deviation, thus maintaining stable average activity. We show that this form of neural heterogeneity endows a network with more flexibility than heterogeneity through variable target firing rates in individual neurons. The increased flexibility in firing rates conferred by diffusive homeostasis resolves the conflict between homeostatic intrinsic plasticity and Hebbian plasticity by limiting the impact of homeostasis on individual synaptic modifications. Consequently, networks endowed with this diffusive mechanism have an improved learning capability compared to canonical, local homeostatic mechanisms, exhibit more stable synaptic weights, and allow for more efficient use of neural resources.

Poster Ref: P2-D-033

Theme: D: Learning, Memory and Cognition

Neural correlates of fear conditioning in the periaqueductal grey.

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The midbrain periaqueductal grey (PAG) is an essential part of the defense–arousal system, controlling the expression of fear–related freezing behaviour (*e.g.* Fanselow 1991). Attention to date has focused on neural pathways underlying autonomic and sensory aspects of PAG activation, and polysynaptic descending paths that modulate autonomic outflow and sensory processing at the level of the spinal cord are well described (*e.g.* Lovick and Bandler 2005). By contrast, much less is known about the patterns of neural activity within the PAG during defence-related behaviours. The present study utilised chronic tetrode recording methods in awake adult rats to study single unit and evoked local field potential (LFP) activity within the dorsolateral and ventrolateral (dl/vlPAG) PAG during the extinction phase of auditory tone conditioned fear. During early extinction trials (when rats displayed significant freezing behaviour in response to the conditioned tone) the response patterns of cells located within both vl/dlPAG could be divided into 3 groups: (i) those that did not exhibit firing rate changes (ii) those that responded with a phasic increase in firing correlated to the onset and offset of the conditioned tone; and (iii) those that displayed a tonic decrease in firing during presentation of the tone. Tone related changes in firing activity were reduced during late extinction trials, when the rats displayed less freezing behaviour. Similarly, evoked LFP responses decreased in amplitude during late extinction. We also found that a number of cells located in both the vl/dlPAG displayed an increase in firing rates when animals were rearing and actively scanning their environment. In sum, extinction learning is linked to a reduction in auditory tone- evoked activity of neurones in the PAG. Together with previous inactivation findings, these results provide evidence that PAG neurones can signal temporal features of a conditioned stimulus necessary to control the expression of associated fear behaviours.

References

Fanselow MS (1991) The Midbrain Periaqueductal Grey Matter: Functional, anatomical and immuno-histohistochemnical organization

Lovick TA & Bandler R (2005) The neurobiology of pain

Poster Ref: P2-D-034

Theme: D: Learning, Memory and Cognition

Dopamine receptor signalling and reactivation of a reconsolidating fear memory.

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Memories are not permanently stable once consolidated; rather, when retrieval is induced by exposure to a reminder cue, the active memory is rendered labile by a destabilisation process. Post-traumatic stress disorder is thought to involve maladaptive persistent memories. A novel therapeutic strategy is to disrupt the memory, when in the active state, with the use of 'amnestic agents' targeting specific neurochemical processes. Fear reminders engage the dopamine system, but the contribution of dopamine signalling to the retrieval and destabilisation of fear memory is not fully understood.

We performed a combination of behavioural testing using Pavlovian fear conditioning and molecular analysis in rodents. The reactivation of a cued fear memory induced activation of the MAPK pathway and Extracellular Regulated Kinase (ERK) in the baso-lateral amygdala, and not it other brain regions as investigated by Western blotting for the phosphorylated form of ERK. We analysed the regulation of this pathway, post memory reactivation, downstream of glutamate and dopamine receptors.

The results will further our understanding of how to achieve diminution of intrusive and maladaptive memories, by identifying molecular mechanisms downstream of dopamine receptor signalling for retrieval and destabilisation of memories.

Poster Ref: P2-D-035

Theme: D: Learning, Memory and Cognition

Multiple questions about a single event in a rodent episodic memory task.

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In rodents, 'episodic-like' memory is modelled in a spontaneous object recognition paradigm in which the animal preferentially explores a novel configuration of object, location, and context. Episodic-like memory and human episodic memory rely on the same neural structures, yet it is difficult to assess whether they are qualitatively similar. In the standard 'object-location-context' (OLC) task, the animal is only required to recall one aspect of a previous episode. Conversely, humans can recall multiple details of past experiences (*e.g.* food items served at breakfast and who was present). Further, human memory is sensitive to retroactive interference; high similarity of prior experiences weakens the ability to remember them as discrete episodes. Therefore, we investigated whether episodic-like memory resembles human episodic memory in that, a) rodents can answer multiple questions about an episode, and b) episodic-like memory is sensitive to similarity-based retroactive interference.

A novel continuous apparatus was used, which permitted multiple trials to be run in succession. In the first experiment, rats (n=8) underwent a version of the OLC task which comprised of four tests, all of which were based on a single sample phase. Animals performed significantly above chance for the first two tests, yet performance diminished on the third and fourth test. This finding demonstrated that rodents can recall multiple details of a single experience, yet memory for the episode is sensitive to retroactive interference. In a second experiment, animals performed above chance on two consecutive dual-test trials, increasing the ability to extrapolate these findings to experimental designs commonly found in rodent memory research.

These results suggest that episodic-like memory is fundamentally similar to human episodic memory in two qualitative dimensions. Further, these results have enormous methodological implications; the time and number of animals required in memory research could be significantly reduced by collecting >1 data point per sample phase and using a continuous apparatus.

Poster Ref: P2-D-036

Theme: D: Learning, Memory and Cognition

State based synaptic plasticity rules in neural networks.

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In the last years synaptic plasticity models have been introduced that have a limited number of discrete states. These models have the advantage that they automatically constrain the synaptic strength while their dynamics are easily manipulated and analyzed in computer simulations. A number of classes of synaptic state diagram has been introduced, such as cascade models, and filter synapses.

In feed-forward networks, the optimal state model that maximized recognition memory performance is known (Barrett and van Rossum). However, while in recurrent network models a limited set of state models was examined, no exhaustive analysis has been performed.

Here we present results which synaptic model maximizes memory capacity.

Poster Ref: P2-D-037

Theme: D: Learning, Memory and Cognition

Dividing attention in complex environments: A fMRI investigation.

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Background: Previous studies indicate that we are able to divide attention between multiple streams of information (divided attention) and that fronto-parietal cortex contributes to this. However, mechanisms of divided attention in real-world scenes are largely unexplored. We used fMRI during the viewing of real-world scenes to study brain activity associated with the monitoring of multiple objects and locations. Our design allowed us also to investigate spatial and non-spatial aspects of attention capture by irrelevant distractors.

Method: Sixteen subjects underwent fMRI during a detection task. They were presented with scenes containing one of two possible object categories (people/cars) located on the left or the right side of the picture. On a block-by-block basis, participants were instructed to monitor one or two categories, in one or both hemifields. The design was 2x2 factorial: spatial attention (Focussed *vs* Divided) and number of relevant categories(1 *vs* 2). Because each picture included only a single person or car, there were also different types of distractors: relevant category at the unattended location and irrelevant category at the attended location. The task was to press a key when an object of the target-category was presented at a target-location.

Results: Behaviourally, subjects were slower when monitoring two objects at two positions (Div-2) compared to all other conditions. Imaging data revealed activation of a dorsal fronto-parietal network for dividing attention between multiple objects. Within the same network, the left frontal eye fields showed maximal activation for the Div-2 condition (interaction). Contrasts between the two types of distractors revealed activation of the right supramarginal gyrus when an object of the relevant category was presented at the unattended location.

Conclusion: Monitoring of multiple object-categories dominated over divided spatial attention and was associated with activation of the dorsal fronto-parietal network. The right inferior parietal cortex mediated the capture of spatial attention when a non-target object (but of a relevant category) was presented at an irrelevant location. We conclude that dorsal and ventral attention systems play distinctive roles to selective processing in complex environments.

Poster Ref: P2-D-038

Theme: D: Learning, Memory and Cognition

Effect of clomipramine and risperidone on cognition in animal model of obsessive compulsive disorder.

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This study builds on a previous study where we have shown that quinpirole (QNP) sensitization in rat, is accompanied by robust deficit in reversal learning. Chronic QNP sensitization is an established animal model of obsessive compulsive disorder (OCD). Currently, effect of clomipramine, risperidone and combination of both was studied on reversal learning deficit.

Clomipramine is an tricyclic antidepressant effective in OCD treatment. Importantly, it also reduces checking behaviour in QNP model. Risperidone is not effective in treating obsessive-compulsive symptoms in patients, but similar antipsychotic (haloperidol) is effective in reducing some of the behavioural effects specific to this model such as counterfreeloading and polydipsia. A combination of SRIs and antipsychotic drugs is effective next choice treatment in patients resistant to traditional SRI monoterapy. Effect of this combination was never tested in animal model of OCD in any context.
In current study we tested an acquisition and reversal learning in QNP induced model of OCD supplemented with clomipramine (10mg/kg), risperidone (0.20mg/kg) or combination of clomipramine and risperidone (10 and 0.20mg/kg respectively). Animal were receiving supplementation/saline and quinpirole/saline 1 hour and 30 minutes, respectively, prior to learning session. Animal were tested on a carousel maze, where animal has to actively avoid a 60º section in the rotating circular arena. After five 30 minute acquisition sessions reversal sessions followed. In reversal to-be-avoided sector was relocated to the opposite side of an arena. Number of entrances into this sector was considered as a main measure of animal learning in both acquisition and reversal.

Results indicate that supplementation of QNP with clomipramine completely disables animals in acquisition learning. Indeed, in these animals the acquisition performance was so inferior that these animals could not be tested in reversal learning (because it would be acquisition again). On the contrary, risperidone and risperidone in combination with clomipramine improved reversal performance equally well in this model of OCD. Yet, performance after this improvement was not comparable to the performance of intact controls.

Poster Ref: P2-D-039

Theme: D: Learning, Memory and Cognition

The effects of a novel positive allosteric modulator of NMDA receptors, UBP709, on synaptic plasticity in the hippocampus.

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NMDA receptors (NMDARs) play a critical role during the development and normal functioning of the brain. They also play a key role in regulating synaptic transmission and in learning and memory. The abnormal expression or activation of NMDARs is implicated in the development of many neuropathological and psychiatric conditions including schizophrenia, in which hypoactivation of NMDARs is thought to be a contributing factor. Excessive NMDAR receptor activation is also a primary cause of cell death in acute neurological insults such as stroke or traumatic brain injury. Use of NMDAR channel blockers or competitive antagonists has reached clinical trials for treatment of neurological disorders but has, with the exception of memantine, thus far been largely unsuccessful. A more recent approach is the development of allosteric modulators that bind to different sites on the NMDAR to those for the agonists and channel blockers and have the potential to modulate the gain of the receptor rather than switch it on or off.

We have developed a number of positive and negative allosteric modulators of NMDARs and recently we investigated the effects of 9-n-butylphenanthrene-3-carboxylic acid (UBP709), on synaptic plasticity at the CA3 to CA1 synapse in rat hippocampal slices. We found that in P14 slices UBP709 enhanced LTD in a concentration dependent manner and reduced the magnitude of LTP. The compound permitted induction of LTD with a 10 Hz paradigm that would not normally induce LTD, and caused a small potentiation of pharmacologically isolated NMDAR fEPSPs. Similarly, UBP709 permitted the induction of robust LTD in adult and aged rats in conditions that are not conductive to evoking LTD. Such induction of LTD was demonstrated to be NMDAR-dependent but independent of mGluRs and GABAA receptors. Using NMDAR subunit preferring antagonists, the facilitation mediated by UBP709 was shown to require the activation of GluN2B containing NMDAR receptors. In conclusion, UBP709, a positive allosteric modulator of NMDARs, may therefore have a use in NMDAR hypofunction disorders.

Poster Ref: P2-D-040

Theme: D: Learning, Memory and Cognition

An examination of hippocampal subfield and entorhinal cortex subsection vulnerability in preclinical dementia using high resolution MRI and cognitive assessments.

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Introduction: The Hippocampus (HC) and Entorhinal Cortex (EC) are vulnerable in AD (1). Global HC atrophy presented with functional decline is considered diagnostic to AD. However, these structures contain distinct subsections hypothesised to be differentially vulnerable in AD (2). We have developed a high-resolution MRI protocol for 3T to determine volumes of HC subsections. We aimed to examine a) volumetric decline and b) cognitive performance of these substructures exploiting cognitive tests sensitive to HC subfield functions.

Methods: 5 mild AD patients, 8 with mild cognitive impairment (MCI) and 8 aged controls undertook cognitive tests. High-resolution MR images were acquired using a 3T Siemens Magnetrom Skyra scanner with in-house written T2-CPMG sequences, TR= 5500ms, echo spacing= 12ms with 12 echoes, slice thickness= 1.72mm, 0.34x0.34mm3 after interpolation, acquisition time= 12 minutes. A segmentation protocol was written to allow the recognition of HC and EC subsection boundaries. Volumetric analysis was performed with FSL software and correlated with cognitive test measures.

Results: 6 HC subfields and 2 EC subsections were identified (Fig 1). Volumes were normalised to total brain volume. A One-way ANOVA with post hoc Bonferroni analysis ($p<0.05$) revealed that atrophy was most pronounced in the CA1 and subiculum HC subfields (Table 1). These subfields correlated the most strongly with cognitive measures, more so than global HC volume (Fig 1).

HC Subfield	Controls vs MCI	Controls vs AD
CA1	0.003	0.001
CA2	1	1
CA3	0.127	0.398
DG	0.335	0.237
SR/SL/SM	0.092	0.06
Subiculum	0.05	0.017

Table 1. ANOVA P-Values obtained between Controls and clinical groups for each HC subfield

Conclusions: The pronounced atrophy of the CA1 and subiculum subfields implies that these are the most vulnerable to early disease effects. Furthermore, their volumes correlated with impaired cognitive performance, thus, they could be a more sensitive measures of pathology than the global HC volume.

References: 1) Devenand DP *et al.* (2012) NeuroImage, 60:1622-1629 2) la Joie R *et al.* (2013) NeuroImage Clinical, 3:155-162.

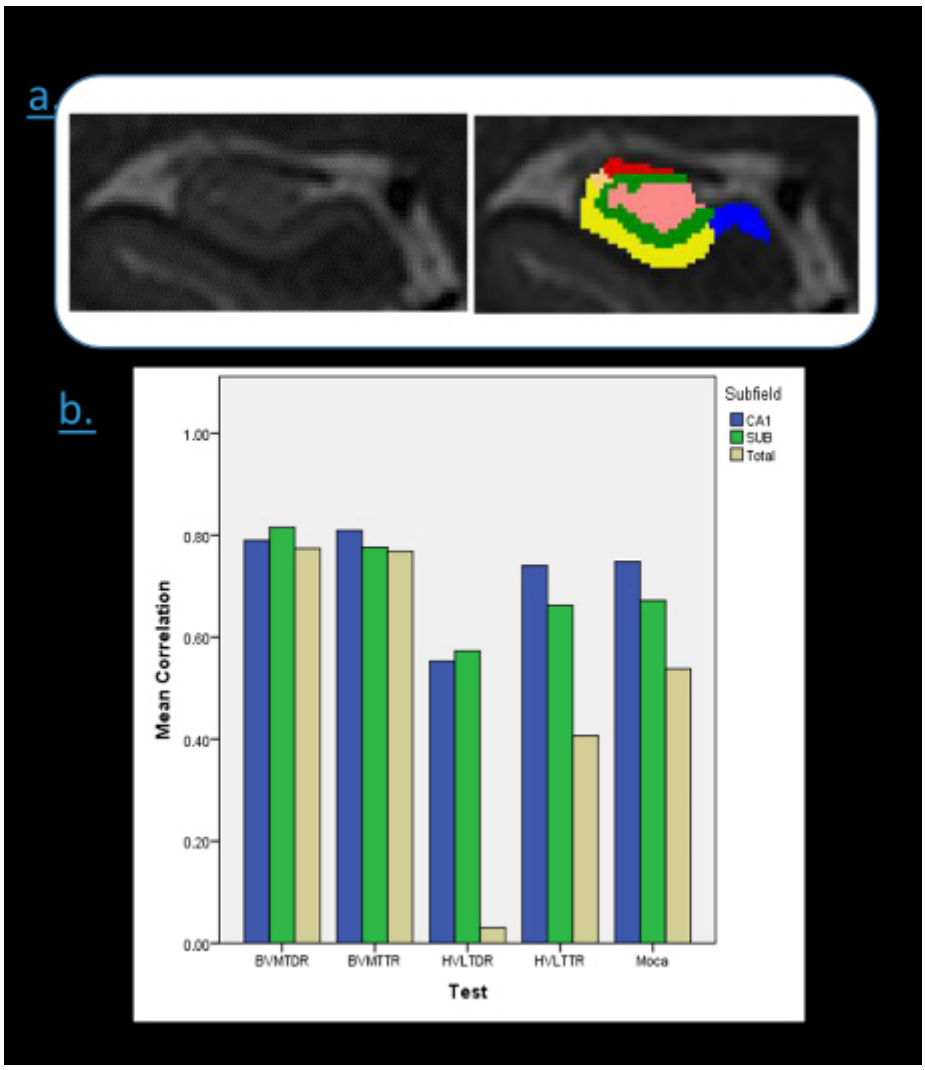

Fig 1. a. A coronal slice through the HC body from an aged control indicating the 6 HC subfields. Yellow= CA1, orange=CA2, red=CA3, pink=dentate gyrus (DG), green= stratum radiatum/stratum lacunosum/stratum moleculare (SR/SL/SM), blue=subiculum. b. Mean correlation of CA1 (blue), subiculum (green) and total HC volume (brown) against cognitive measures.

Poster Ref: P2-D-041

Theme: D: Learning, Memory and Cognition

Selective silencing of medial prefrontal parvalbumin interneurons recapitulates positive, negative and cognitive schizophrenic symptoms in mice.

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Multiple lines of evidence point to dysfunction of parvalbumin positive interneurons (PVIs) in the dorsolateral prefrontal cortex (DLPFC) as a core component of human Schizophrenia (SZ). As the DLPFC is a key regulator of both working memory (WM) and pre-pulse inhibition of startle reflex (PPI) this hypothesis is in accordance with WM and PPI deficits observed in SZ patients.

To evaluate this hypothesis we generated a prospective mouse model of SZ *via* selective cell silencing of PVIs in the rodent medial prefrontal cortex (mPFC), the rodent analogue of the human DLPFC. This was achieved by a bilateral intracerebral injection of a novel cre dependent adeno-associated virus (AAV) into the mPFC of mice expressing cre recombinase under the parvalbumin promoter. AAV payload consisted of either green fluorescent protein (GFP) only (control) or in combination with tetanus toxin light chain (TeLC). PPI was assessed using mouse acoustic startle chambers while visuo-spatial working memory was assessed using a Barnes' maze paradigm including both an acquisition and a reversal phase. An analysis of circadian activity was performed over a 72 hour home cage activity recording.

PPI was found to be significantly reduced in animals infused with TeLC-AAV relative to GFP-AAV only controls. No group differences were detected during acquisition training or in acquisition probe performance. During reversal TeLC-AAV animals displayed a significantly faster reduction in mean path length and escape latency than GFP controls. Paradoxically the TeLC-AAV group performed poorly during the reversal probe trial indicating a deficiency in target recall. A secondary analysis of search strategy demonstrated that this effect is entirely explained by a failure to adopt spatially oriented search strategies by the TeLC-AAV group during reversal. Instead they preferentially performed a sequential search of a number of potential target locations before locating the target by chance. Circadian activity analysis indicated modest TeLC-AAV hyperactivity during dark hours (active period) with no group differences in light phase activity. Cumulatively the results indicate that a selective silencing of only PVIs in the rodent mPFC alone is sufficient to induce several features of the SZ phenotype.

Poster Ref: P2-D-042

Theme: D: Learning, Memory and Cognition

Interaction between brain systems of executive control and error detection underlying goal-directed behaviour in deception.

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Deception can be defined as “a successful or unsuccessful deliberate attempt, without forewarning, to create in another a belief that the communicator considers to be untrue” (Vrij, 2008). In order to deceive an opponent one need constantly keep in mind the goal to mislead an opponent, continuously select between truthful and deceptive actions and monitor their performances. Therefore deception is a convenient experimental paradigm to study mechanisms of goal-directed behaviour.

Based on contemporary literature, execution of deception is usually associated with fronto-parietal neuronal brain network (including anterior cingulate cortex (Abe *et al.*, 2008; Ganis, G., Keenan, J.P., 2009; Christ, *et al.*, 2009; Kireev, *et al.*, 2013), which is also responsible for the wide range of tasks in which cognitive efforts are needed for proper execution of ongoing activity. Indeed in a number of recent studies a consistent contribution of the fronto-parietal brain network to the both deceptive and honest actions was shown (Abe *et al.*, 2014; Kireev *et al.*, 2013; Sip *et al.*, 2010). Along with that, functional activity specifically associated with deception was revealed in caudate nuclei (CN, Kireev *et al.*, 2013), the location where the first physiological evidence of error detection (ED) reaction was observed by Bechtereva (1968).

Taking all those findings into account we hypothesized that ED system is responsible for performance monitoring of both honest and deceptive actions, but interacting at a greater extend with executive control network when deception is executed. This proposition was checked by application of psychophysiological interaction analysis (PPI) of fMRI data from 24 healthy subjects, which gives an opportunity to observe how the functional interplay between involved brain regions is changed as a function of the psychological context. As a result we revealed that deceptive actions were associated with relatively greater functional interaction within left prefrontal cortex, *i.e.* between middle frontal gyrus and inferior frontal gyrus (IFG), and between left IFG and CN. Observed findings can be considered as an example of interaction between ED and executive control systems underlying goal-directed behaviour.

Poster Ref: P2-D-043

Theme: D: Learning, Memory and Cognition

The influence of novelty on risk-taking behaviour.

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Aims: Novelty preference or sensation seeking is an important trait related to initiating and maintaining risky behaviours, including substance abuse. Here we introduce a novel or familiar prime (image) preceding a risk choice and focus on behavioural and imaging correlates to the prime that might predict risk seeking in healthy volunteers. We aim to investigate whether novel or familiar primes affect judgments of risk. We hypothesize that subjects would be more risk seeking following a novel relative to familiar stimulus and that subjects who are more novelty seeking will have increased striatal and hippocampal activity to the novel stimulus.

Methods: We adapted a risk-taking task involving acceptance or rejection of a 50:50 choice of gain or loss which was preceded by a familiar (pre-test familiarization) or novel face prime. Neutral expression faces of males and females from The Karolinska Directed Emotional Faces database were used as primes. Subjects were tested behaviourally and scanned using functional MRI as they were performing a different version of the same task.

Results: Twenty-four healthy volunteers were recruited for the behavioural study and eighteen for the fMRI study. We show enhanced risk taking following novel relative to familiar images and particularly for the low gain condition. Subjects had faster reaction times to the prime when accepting rather than rejecting the risky choice. We further show that right putamen activity to novel versus familiar primes were positively correlated with risk taking choices

Conclusions: Novelty appears to have a contextually enhancing effect on augmenting risky choices possibly mediated *via* putaminal activity. These findings highlight the role of context in risk taking and have important implications for a wide range of behaviours including substance abuse.

Poster Ref: P2-D-044

Theme: D: Learning, Memory and Cognition

Morris water maze training-induced epigenetic modifications and gene expression changes in rat dentate gyrus neurons.

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Exposure to an acutely stressful event leads to activation of NMDA receptors, initiating a cascade of MAPK/ERK signalling, epigenetic modifications and immediate early gene (IEG) induction in sparse neurons of the dentate gyrus (DG). These changes have been shown to be vitally important for long-term memory formation of the stressful event (Gutierrez-Mecinas *et al.* 2011 PNAS 108: 13806-13811). In this study, this signalling pathway is explored in the context of the Morris water maze (MWM), a moderately stressful challenge whereby rats learn to find a hidden platform in a pool of water. Lister-Hooded rats were exposed to five trials (one free swim trial (3min), 4 training trials (≤3min); inter-trial time: 10min) in the MWM; mRNA analysis and immunohistochemistry were then used to investigate signalling, epigenetic, and IEG changes in the DG of the rat hippocampus during and after MWM training. The molecular responses of rats undergoing the MWM training protocol were compared with baseline animals and with time-matched swim controls (SC) which did not actively learn a platform location. MAPK/ERK signalling, formation of the histone H3S10p epigenetic mark and IEG induction occurred within sparsely distributed DG neurons in both MWM-trained and SC rats to a remarkably similar extent. Chromatin immuno-precipitation studies are currently underway to investigate the role of this epigenetic modification in IEG transcription after both conditions. Next, we conducted RNA sequencing analysis on DG mRNA samples collected from rats under baseline conditions, 3hr or 7hr after the start of MWM or SC. Preliminary analyses show that at 3h, compared with baseline, MWM and SC showed 252 and 74 differentially expressed genes respectively; whereas at 7h these gene numbers were 56 and 129. Further study is required in order to determine the role of differentially expressed genes in spatial memory formation in the MWM.

Poster Ref: P2-D-045

Theme: D: Learning, Memory and Cognition

Concurrent monitoring of multiple prospective memory targets: the impact of increased load on the ongoing-task.

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Introduction: Prospective memory (PM) defines the capacity to form, maintain and remember intentions to perform future actions. Standard paradigms entail a PM-target monitoring phase, filled with an ongoing task (OT), and a PM-target detection phase when the action takes place. Here we asked how the presence of multiple concurrent PM tasks influences the PM monitoring process. This is relevant for real-life situations that involve maintaining several different prospective intentions at once. We compared brain activity associated with an OT, while participants monitored either one or two PM targets. We hypothesized that performing two concurrent PM tasks would increase the PM monitoring load and modulate brain activity associated with the OT.

Methods: Before fMRI scanning, participants received instructions about the OT and one of the two PM tasks (PM1), which they then had to perform throughout the session. The stimulus-display included 4 colored letters. The OT involved pressing one of two buttons to indicate left/right position of the OT-target letter (presented in all trials). The PM1 involved responding to a different letter by pressing a third button as soon as this was detected (PM1-target, 5% of the trials). The PM2 was cued on a block-by-block basis and involved monitoring a specific color, again pressing the third button when this appeared (PM2-target, 5%). The main imaging analysis compared OT-related activity when participants monitored both PM1 and PM2 targets (high load) vs. when they performed the PM1 task only (low load).

Results: Participants were faster and more accurate in the low than the high load condition, both for the OT position-discrimination and for the PM1 target-detection. The fMRI analyses of the OT trials revealed larger de-activation of the medial frontal cortex (including BA10) in the high compared to the low load condition, and an activation of the intra-parietal sulcus in the high load condition.

Conclusion: The manipulation of PM monitoring load, *via* the inclusion of multiple concurrent PM tasks, was found to affect ongoing processing, with a modulation of activity in medial frontal and parietal cortex. These results highlight an interplay between monitoring and attention mechanisms in complex high demanding PM situations.

Poster Ref: P2-D-046

Theme: D: Learning, Memory and Cognition

Influence of inhibitory and excitatory synaptic strengths and noise on grid firing and gamma oscillations in a spiking continuous attractor network model.

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Cognitive functions are often associated with changes in gamma frequency oscillations and may involve fine-tuning of synaptic strengths. However, clear mechanistic relationships between synaptic strength, gamma oscillations, and neural computations underlying cognition have not been determined. We explore these relationships by systematically varying recurrent synaptic strengths in a spiking continuous attractor network model that can generate both grid firing fields and theta-nested gamma oscillations through a shared synaptic mechanism. We find that both the stability of grid firing fields and properties of nested gamma oscillations are sensitive to changes in the strength of excitation and inhibition. However, gamma oscillations carry relatively little information about the gridness score of the spatial firing fields or the ability of the networks to form a continuous attractor state. This suggests that it might not be possible to predict whether a network successfully encodes position by measuring the amplitude or frequency of gamma oscillations. Instead, robust grid firing fields generated by the attractor networks are compatible with a wide range of gamma oscillation amplitudes and frequencies. Unexpectedly, we find that moderate neural noise promotes generation of both gamma oscillations and grid field computation. The range of synaptic strengths supporting gamma oscillations and spatial firing fields with high gridness score is greatly increased with moderate noise. This effect is attributable to noise desynchronizing the epileptic-like states present in noise-free networks. Our results suggest that gamma oscillations and grid firing might have independent roles during cognitive processing and also highlight the beneficial effect of noise on neural computation.

Poster Ref: P2-D-047
Theme: D: Learning, Memory and Cognition

ERP correlates of learning.

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Someone's current knowledge about words and objects can be measured with the N400 event-related potential (ERP). The N400 is a classic ERP component indexing semantic processing and is more negative in amplitude the less a word or picture of an object is expected in a specific semantic context. Here I report a study investigating whether learning the meaning of unfamiliar words has an online regressive effect on N400 amplitude. Participants were presented with sentences beginning with unfamiliar words. The sentences were either providing meaning or no/little meaning of the words (e.g., meaningful: An ephemeris gives the relative positions of astronomical objects.; providing little meaning: An ephemeris app can be downloaded onto a phone for mobile use.). After this learning phase, the words were embedded in a classic sentence-final position to measure the extent to which the words were learned -as reflected in N400 amplitude elicited by this word. The results show a clear learning effect for words presented with meaningful definitions as compared to words presented with meaningless definitions. During the learning phase, the ERPs elicited by unfamiliar words gradually differentiated depending on whether the previous word's definitions had been meaningful or meaningless. The increase in knowledge about a word was reflected by decreasing N400 amplitude extending to a late (600-800ms) positivity at centroparietal electrode sites. These results show that the process of learning is reflected online in brain potentials.

Poster Ref: P2-D-048

Theme: D: Learning, Memory and Cognition

Investigating roles of entorhinal-hippocampal circuits in path integration.

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Successful storage and recall of spatial memories relies on accurate estimation of location. This can be achieved through multiple distinct strategies including use of landmarks or by path integration, which involves inference about location from direction and distance moved relative to a known start point. The extent to which animals can use path integration to solve spatial memory tasks is unclear and designing tasks that dissociate path integration from other strategies is challenging. The roles of specific cell types are also unknown. Within the hippocampal-entorhinal circuit, place, grid, head direction and border cells encode information that can be used to estimate location. The extent to which these cell types contribute to path integration or other strategies for solving spatial tasks is still unclear. To investigate these issues, we developed a spatial memory task for mice, which uses virtual reality to generate sensitive measures of an animal's ability to path integrate. We show that in this task wild-type mice can locate a reward zone using either proximal cues or a path integration strategy. To test roles of identified cell types in the task we injected adeno-associated virus expressing the light chain of tetanus toxin, conditionally in the presence of Cre, into the brains of mice expressing Cre under the control of promoters with activity restricted to particular cell types. We find that inactivation of principle cells within CA1, subiculum and MEC interferes with performance of the spatial task. Our data establish a novel behavioural test for spatial learning in which roles of landmark cues and path integration can be dissociated. We provide evidence that entorhinal-hippocampal circuits are required for successful performance of this task.

Poster Ref: P2-D-049

Theme: D: Learning, Memory and Cognition

The voltage-independent activity of GluN2A-containing NMDA receptors causes severe cognitive disorders and audiogenic seizures followed by respiratory arrest in mice

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Voltage dependent gating of N-methyl-D-aspartate receptors (NMDARs) is essential for excitatory synaptic transmission and activity-dependent neuroplasticity. Here we removed the voltage dependent Mg^{2+} block of GluN2A subunit-containing NMDARs by gene targeted insertion of the Grin2A(N596S) mutation in mice. The mutation is homologous to a human de novo point mutation found in a young patient with severe mental retardation and epileptic seizures. Homozygous Grin2AS/S mice for the Grin2A(N596S) mutation showed profound impairments in cognitive functions and exhibited 100% penetrance of generalized convulsive seizures induced by acoustic stimuli, which lead to seizure-induced respiratory arrest. The seizure induction could be blocked by NMDARs antagonists, indicating that the activation of the mutated receptors is directly involved in the formation and spreading of altered electrical activity. In heterozygous Grin2AS/+ mice the mutation had a lower penetrance and the epileptic phenotype could be observed in about 25% of the mice, independently of age or gender.

Thus we experimentally verified that the voltage-dependent signaling of the GluN2A-containing NMDARs is crucial for learning and cognitive functions and normal electrical activity. Moreover, compared to the existing animal models for suddenly unexpected death in epilepsy (SUDEP), the homozygous mouse for the mutation could be a better model for further research and for evaluating potential therapies.

Poster Ref: P2-D-050

Theme: D: Learning, Memory and Cognition

Investigating links between use of technology and cognitive reserve in the aberdeen birth cohort of 1936 (ABC1936).

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Introduction: Cognitive reserve (CR) is a moderator which allows the preservation of cognitive functions despite brain pathology. No studies have addressed how the use of technology in later life contributes to CR, despite a rapid increase in technology use and the possibility of using technology-based interventions. This study links cognitive and imaging biomarker data with information on technology use in an elderly population to determine whether technology use can attenuate the negative effects of neuropathology on cognitive functions.

Methods: New data on technology use was obtained using a modified version of the Computer and Technology Experience Questionnaire which supplements existing resources on imaging biomarkers and cognitive tests from the ABC1936. All living members of the Cohort (n=378) were invited to participate *via* a postal questionnaire. Summary measures of technology use for different purposes were calculated. CR was modelled as the residual variance from the regressions of cognition [Auditory Verbal Learning Test (AVLT) and Raven's Progressive Matrices non-verbal reasoning test (RPM)] on separate measures of brain pathology [MRI quantification of brain fraction, hippocampal fraction and white matter hyperintensities (WMH)]. Next, the CR residual was regressed on the hypothesized determinants of reserve (facets of technology use, education, occupation).

Results: Questionnaires were returned by 131 people, 80 of whom also had cognitive and MRI data. Most respondents (75%) reported experience with IT and 67% viewed it favourably. Preliminary analyses (Table 1) show that certain measures of technology use were significantly associated with the non-verbal reasoning test CR residuals across different pathologies, including total technology use and use in leisure and education activities. Computer use was significantly associated with CR residual originating from regressing verbal memory score on hippocampal and brain fractions. Education was significantly associated with non-verbal reasoning CR residual across multiple pathologies after adjustment for childhood IQ and gender.

Conclusion: In addition to education and occupation, greater technology use potentially contributes to CR and helps retain cognitive function in late-life.

Relationships between determinants of reserve & CR residuals*		Cognitive tests			
		Verbal Memory (AVLT)	AVLT adjusted**	Non-Verbal Reasoning (RPM)	RPM adjusted**
Determinant of reserve	**Measure of brain pathology**	**P**	**P**	**P**	**P**
Total technology use	Hippo Fraction	NS	-	< 0.05	NS
	Brain Fraction	NS	-	< 0.05	NS
	WMH	NS	-	< 0.05	NS
Technology use in leisure	Hippo Fraction	NS	-	< 0.05	NS
	Brain Fraction	NS	-	< 0.05	NS
	WMH	NS	-	NS	-
Technology use in education	Hippo Fraction	NS	-	< 0.05	NS
	Brain Fraction	NS	-	< 0.05	NS
	WMH	NS	-	< 0.05	NS
Computer use	Hippo Fraction	< 0.05	NS	NS	-
	Brain Fraction	< 0.05	NS	NS	-
	WMH	NS	-	NS	-
Education	Hippo Fraction	< 0.05	NS	< 0.05	< 0.05
	Brain Fraction	< 0.05	NS	< 0.05	< 0.05
	WMH	NS	-	< 0.05	< 0.05
Occupational	Hippo Fraction	NS	-	< 0.05	NS
	Brain Fraction	NS	-	< 0.05	NS
	WMH	NS	-	< 0.05	NS

Table 1: Results of multiple linear regressions: relationships between CR residuals and determinants of reserve. * CR residuals captured by regressing cognitive ability scores on separate measures of brain pathology. ** adjusted for gender and childhood IQ. AVLT = Auditory Verbal Learning Test. RPM = Raven's Progressive Matrices.

Poster Ref: P2-D-051

Theme: D: Learning, Memory and Cognition

Synaptic depression enables reliable sequential activity cascades in recurrent networks.

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A growing body of research reports the sequential activation of neural assemblies, suggesting that some brain computations are performed through sequence-based dynamics. It remains unclear how those sequences are generated and a number of models have been proposed. Kremkow *et al.* (J. Neurosci 2010) demonstrated that timing differences between correlated excitation and inhibition - temporal gating - can control the propagation of spiking activity transients. We adapted this mechanism in the following scenario. We simulated a recurrent balanced network of 20,000 conductance-based leaky integrate-and-fire with sparse connectivity (5%) and embedded a chain of gates, exploiting the temporal gating principle. The chain consisted of 3 to 20 gates to test whether this framework can underlie the generation of sequential activity in the spiking networks. We found that this connectivity enables, in principle, reliable feed-forward propagation and transient amplification along such a chain. However, in a recurrent network the synchronous activity in a chain can also excite the rest of the network, which then leads to instabilities such as persistent oscillatory activity. If the total excitation is weaker to compensate for such effects, the network elevates its activity during the signal propagation which is followed by the period of hyperpolarization of most of the neurons. On the network level it can be interpreted that the activation of a chain destabilizes and then transiently shuts down the whole network. We next investigated the possible role of two mechanisms in stabilising network activity under these conditions. Spike Frequency Adaptation did not prevent the network from entering the oscillatory regime but allowed it to escape it and return to its normal state. Short-term plasticity in a form of synaptic depression allowed the network to remain in its stable state and shortened the hyperpolarization following chain activation. Next, we plan to extend the model by adding various interneuron types, particularly fast-spiking PV+ interneurons, to investigate whether different modes of inhibition can stabilize the network and extend its robustness.

Poster Ref: P2-D-052

Theme: D: Learning, Memory and Cognition

Exploring the relationship between episodic memory, future thinking and scene construction in pre-schoolers.

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‘Mental time travel’ is the ability to mentally project oneself into to the past and future, in order to recollect past experiences and imagine future episodes (Suddendorf & Corballis 2007). It has been suggested that these forms of episodic cognition are intimately linked (Schacter & Addis 2007). Evidence for a common or overlapping mechanism comes from neuroimaging studies, lesion studies and correlated changes in aging (Buckner & Carroll, 2007). The explanation for this link at a cognitive level is debated, but one popular notion is that both draw upon the cognitive skill of scene construction (Hassabis *et al.*, 2007). In order to explore this hypothesis we looked at individual differences in imagination, memory and planning over child development.

We conducted a test battery with children between four and six years of age: including a ‘spoon test’ of memory and planning from Atance & Sommerville (2014) and interviews modified from Hassabis *et al.* (2007). In the interviews, participants were provided with a prompting context (*e.g.* zoo) in one of three tenses (past, present and future). For example, they were told to either “Think of a time when you went to a zoo”; “Pretend you are at a zoo right now”; or “Imagine that you are going to a zoo tomorrow”. Each child described 6 events: the order of tense presentation and the context used in each tense was counterbalanced across participants. Transcripts were coded for description content and quality. After testing 29 children from local nursery and preschools, significant improvement between four and five years of age was shown across both tasks and across all tenses. Strong correlations were found between scores in all three tenses after controlling for age and verbal IQ, providing support for the notion that a common mechanism supports the construction of scenes in the past and future, as well as in the present. However, performance in the future tense was weaker than that in the past and present hinting at distinct cognitive challenges associated with imagining future events.

Poster Ref: P2-D-053

Theme: D: Learning, Memory and Cognition

Distinct contributions to associative recognition memory formation by cholinergic muscarinic receptor subtypes 1 and 2 in the medial prefrontal cortex.

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Associative recognition memory formation, the ability to associate objects with specific locations, requires the medial prefrontal cortex (mPFC) (Barker & Warburton 2007, 2011). Muscarinic receptor activation in the mPFC is essential for associative recognition memory formation (Barker & Warburton 2008), however the specific role of the M1 and M2 muscarinic receptor subtypes has not yet been addressed. Therefore this study assessed the contribution of the M1 and M2 muscarinic receptor subtypes within the mPFC to the encoding and consolidation of associative recognition memory. Male Lister-hooded rats were implanted with bilateral guide cannula aimed at the mPFC. To assess the role of M1 and M2 receptors in associative recognition memory the selective M1 antagonist VU0255035 (1μM/side) or the M2 selective antagonist AF-DX116 (2.5mM/side) were infused at different time points during the object-in-place task (Dix & Aggleton 1999). In order to assess the role of each subtype in encoding or consolidation the subtype selective antagonists were infused, either 15 min before the sample phase (encoding) or 2 min after the sample phase (consolidation).

Infusion of either VU0255035 or AF-DX116 into the mPFC before the sample phase impaired the encoding of object-in-place memory tested at a 3h delay. Infusion of VU0255035 after the sample phase had no effect on object-in-place memory however infusion of AF-DX116 after the sample phase enhanced object-in-place memory.

These results demonstrate that the encoding of associative recognition memory is dependent on the activation of both M1 and M2 receptors within the mPFC. In contrast consolidation of associative recognition memory is enhanced by blockade of M2 receptors, but M1 receptors appear not be involved. These results provide a potential insight in to the modulatory role of cholinergic neurotransmission *via* muscarinic receptors during memory encoding and consolidation, and specifically that these processes may require fluctuations in levels of acetylcholine within the mPFC.

Poster Ref: P2-D-054

Theme: D: Learning, Memory and Cognition

Dopamine neuron numbers, impulsivity and risky decision making in rats.

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There are well-developed theories describing how the brain adapts behaviour to obtain reward, but relatively less is known about how the brain encodes resource loss and risk. Previous tests in animals have struggled to effectively operationalise resource loss, using instead opportunity costs or outright punishment as the risky outcome. Therefore, we developed a novel risky decision-making task in which thirsty rats earn or lose a liquid reward by nosepoking in 1 of 3 nosepoke holes. Similar to the human BART task (1), more reward was given for longer nosepokes, but longer nosepokes also increased the risk of reward omission. Therefore, at each moment of a poke, a rat was confronted with the dilemma of whether to: (A) continue poking for more reward and risk losing it all, or (B) unpoke and consume any reward accrued up to that point. Levels of risk and reward accrual varied across the 3 nosepoke holes, which revealed preferences in trade-offs between risk and reward. Rats were classified into two groups (impulsive or patient) based on their preference for small-safe or large-risky rewards. Average nosepoke durations, choices, and stay-shift behaviour were significantly affected by task manipulations and the outcome of the previous trial. Dopamine antagonist Flupenthixol was administered in 3 doses to assess dopamine's role in risky decision making. After testing, rats' midbrains were stained for tyrosine hydroxylase (TH). Counts of TH-stained neurons were conducted for the ventral tegmental area and substantia nigra. Impulsive *vs*. patient rats and loss-stay behaviour significantly correlated with neuron counts in the substantia nigra. When the vehicle was given, rats with more substantia nigra dopamine neurons chose the same hole after a loss more often (loss-stay). Systemic dopamine blockade abolished this effect at both the low and high doses. In conclusion, despite a variety of potential neuromodulatory mechanisms, the decision to return to a previously chosen option after a loss strongly correlates with the number of midbrain dopamine neurons in rats. Thus, variation in the anatomical characteristics of the dopamine system may offer some insight into individual differences in risky decision-making behaviour.

(1) Lejuez,CW *et al.* 2002. J Exp Psychol 8:75-84

Poster Ref: P2-D-055

Theme: D: Learning, Memory and Cognition

Neuromodulation of prefrontal cortical and the hippocampal networks following optogenetic stimulation of ventral tegmental area dopaminergic projections.

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Dopamine (DA) is released in the prefrontal cortex (PFC) from the ventral tegmental area (VTA) during different aspects of cognition, including reward and mnemonic processing. Dopaminergic modulation of PFC network activity has been extensively studied using pharmacology, leading to various models of the role of DA in working memory. However, the *in vivo* effects of physiological DA release on PFC network activity and the PFC's interactions with afferent structures including hippocampus remain to be established.

Optogenetics is an ideal tool to induce physiological DA release in the PFC. We adapted a model using the adeno-associated viral vector AAV5-DIO-ChR2-EYPF in transgenic TH-cre rats to express channelrhodopsin in midbrain dopaminergic neurons. We combined optogenetics with chronically implanted tetrodes in the prelimbic cortex and the CA1 region of the dorsal hippocampus, from which we recorded both local field potential (LFP) and the single unit activity.

Here we present data confirming the efficacy of optogenetics in a self-stimulation task (N=5), as well as preliminary results of the recordings in resting rats of PFC and CA1 network activity in response to the same VTA stimulation parameters able to support self-stimulation. VTA stimulation induced heterogeneous effects on putative pyramidal cell firing rates, rhythmicity (particularly 5-10Hz theta modulation), and bursting properties of neurons recorded in both the PFC (N=36) and hippocampus (N=92). At a population level, neighbouring neurons recorded on the same tetrode tended to fire more synchronously following VTA stimulation.

These results indicate a heterogeneity of neural responses to VTA stimulation, compatible with the neuromodulatory roles of DA and its diverse actions on different receptor and neuron types. We are currently assessing the state-dependence of DA's effects on CA1-PFC interactions in a range of behavioural contexts.

Poster Ref: P2-D-056

Theme: D: Learning, Memory and Cognition

Active Subthreshold Synaptic Integration by Neurons in the Inferior Olive.

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The inferior olive is a key component of the olivocerebellar circuit critically involved in timing and co-ordination of movements. Diverse inputs, including descending cortical and ascending sensory signals, are integrated within the olive to generate the climbing fibre projection to the cerebral cortex. While much is known about the importance of this projection for motor co-ordination, we know relatively little about how olivary neurons generate meaningful output from the diverse inputs that they receive. Computational models have made testable predictions on how neuronal computations are performed within these networks. The models suggest that, above a certain threshold synaptic input triggers calcium dependent biphasic responses. We sought to test this hypothesis by targeting channelrhodopsin (ChR2) to long-range projection neurons and recording olivary responses to these inputs. We find that activation of long-range inputs generates rapid excitatory potentials followed by slower inhibitory potentials. These biphasic responses are dependent upon GluA receptors, but are GABAA independent. Responses lack the inhibitory component when HCN1 channels are blocked, suggesting that HCN1 channels maintain dendritic depolarisation at a sufficient level to elicit biphasic responses. We confirmed that biphasic responses require electrical coupling by blocking gap junctions, which blocked the biphasic response. We also prevented the generation of biphasic responses by targeting calcium-activated potassium channels, suggesting a role for locally generated calcium spikes. In conclusion, our data provide evidence for active integration of synaptic responses by neurons in the inferior olive.

Poster Ref: P2-D-057

Theme: D: Learning, Memory and Cognition

Interferon induced changes in amygdala processing of emotional faces predict subsequent development of depressive symptoms.

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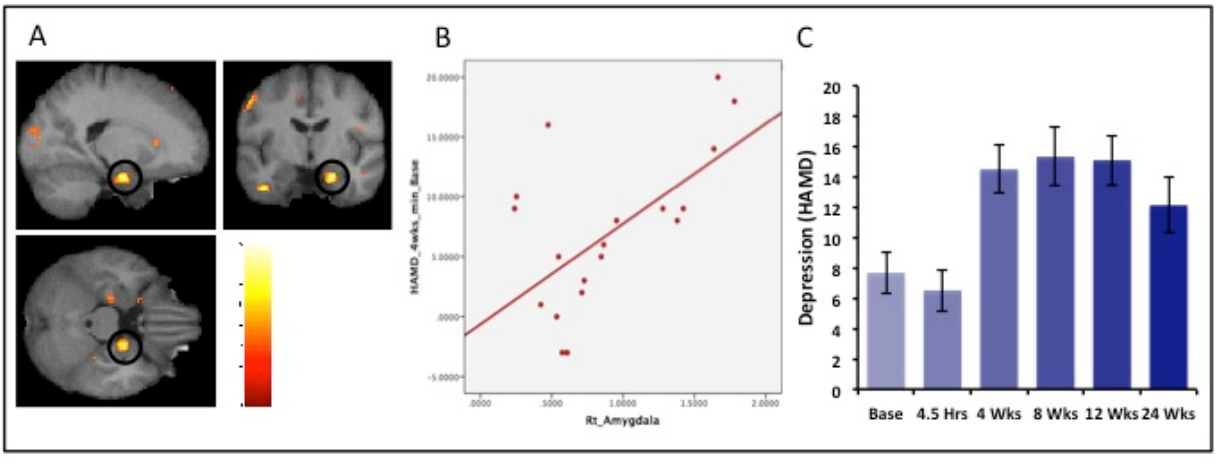
Inflammation is increasingly implicated in the aetiology of depression. Observation that 1/3 patients receiving Interferon-α (IFN, a pro-inflammatory cytokine) for hepatitis-C subsequently develop depression is key supporting evidence for this 'inflammatory theory of depression'. Previous studies show functional changes in brain regions implicated in emotion processing during interferon-induced depression. However, whether acute actions of IFN predispose individuals to the subsequent development of depression is unknown.

We therefore tested 20 patients (mean 48.2 years (sd. 11.2), 15 male) on an emotional face-processing task, before and 4 hours, after their first IFN injection then followed them up for 6 months. Participants observed 111 unique happy, sad and neutral face stimuli during each fMRI session, with speeded response to indicate experience of the shown emotion in the prior 24 hours.

IFN significantly increased depression symptoms (HAMD) at 4 weeks ($t=4.48$, $p<0.001$). No change in emotional experience rating or HAMD was observed at 4 hours ($p>0.05$) though response times to happy faces were significantly slowed post IFN ($t=2.38$, $p=0.028$). As anticipated, viewing face stimuli activated the ventral visual stream including bilateral fusiform face areas and amygdala regions of interest (whole ROI $p<0.05$). Significantly greater amygdala activity was observed to emotional vs. neutral stimuli (ROI $p<0.05$), with significantly reduced left amygdala reactivity to happy compared to neutral faces post IFN (ROI $p=0.026$) and converse increase in right amygdala reactivity to sad compared to neutral stimuli (ROI $p=0.037$). Changes in right amygdala reactivity additionally predicted increase in HAMD depressive symptoms 4 weeks later (ROI $p=0.006$, $R2=0.32$).

We demonstrate that IFN acutely modulates amygdala reactivity to positive and negatively valenced face stimuli and further that this increase in right amygdala response to sad (versus neutral) stimuli predicts the development of depressive symptoms 4 weeks later. Interestingly, though explicit ratings of emotional experience and depressive symptoms (HAMD) were unchanged at 4 hours, response times to happy faces were prolonged suggesting an action on implicit behavioural responses to positively valenced stimuli.



A. Right amygdala increase in reactivity to sad versus neutral face stimuli after IFN. B. Correlation change in HAMD and right amygdala response to sad versus neutral stimuli. C. Change in HAMD score after IFN.

Poster Ref: P2-D-058

Theme: D: Learning, Memory and Cognition

Acyl-Ghrelin and calorie restriction induce immediate early gene (IEG) expression in the adult hippocampus: implications for learning and memory.

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Calorie restriction (CR) has a beneficial effect on cognitive function. However, the mechanisms that mediate this are not well characterised. Circulating levels of the orexigenic hormone, acyl-ghrelin (AG), were shown to be elevated during CR and AG is known to positively modulate learning and memory processes. Conversely, all other known gastrointestinal hormones are elevated following feeding to promote satiety. Therefore, AG may, at least in part, mediate the beneficial effects of CR on mnemonic function.

In this study, we have characterised the expression of the ghrelin receptor, GHSR, in extra-hypothalamic regions such as the dentate gyrus (DG), lateral entorhinal cortex (Lent), cingulate cortex (CC) and basolateral amygdala (BLA). Here we have utilised GHSR-eGFP reporter mice to confirm that GHSR is expressed in these regions. Using the same mouse line we show that GHSR (GFP+) was extensively expressed on mature DG (NeuN+) granule cell neurones. In contrast, we did not observe co-localisation of GFP+ with either type I (Nestin+) or type II (Sox2+) neural stem/progenitor cells (NSPCs) in the DG. Furthermore, proliferating (Ki67+) cells were not co-localised with GFP in the sub-granular zone of the DG. These data suggest that AG does not mediate direct effects on NSPC's.

Subsequently, we investigated the effect of AG on expression of IEGs, Egr-1 and c-Fos, in adult GHSR-eGFP mice. We raised AG levels directly *via* injection (10ug/kg i.p), indirectly *via* CR (overnight fast), or with injection and CR. 16h after directly elevating AG, expression of Egr-1 was increased in the DG, CC ($P<0.01$), BLA and CA1 ($P<0.05$). CR elevated Egr-1 expression in the DG and BLA ($P<0.05$), whilst the combination of AG and CR also increased Egr-1 expression in CC and BLA GHSR-GFP+ neurones ($P<0.01$). Conversely, c-Fos expression was only increased in CC ($P<0.01$) and DG-SGZ ($P<0.05$) GHSR-GFP+ neurones after AG treatment. However, we did observe a significant decrease in c-Fos in the hilus after CR ($P<0.05$), AG ($P<0.01$) and combined AG/CR ($P<0.01$). Furthermore, c-Fos expression was also decreased in the Lent ($P<0.05$) after both AG treatment and CR.

These data suggest that the pro-neurogenic transcription factor Egr-1 is responsive to AG and CR in brain regions involved in cognition.

Poster Ref: P2-D-059

Theme: D: Learning, Memory and Cognition

The effect of minocycline on hippocampal and non-hippocampal memory systems: an fMRI study in healthy humans.

Sam Berens[1], Maud Plouvier[2], Chris Bird[1], Christian Doeller[2] and Neil Harrison[3]

[1]University of Sussex, UK, [2]Radboud University Nijmegen, Netherlands, [3]Brighton and Sussex Medical School

Background: Neuronal-microglial interactions in the medial temporal lobes (MTL, particularly the hippocampus) are believed to regulate learning and memory processes such as LTP, LDP and neurogenesis. Minocycline (a tetracycline antibiotic) crosses the blood-brain barrier and is known to inhibit microglial activity *via* mechanisms distinct from its antimicrobial action. Aberrant microglial over-activity has been implicated in various neurodegenerative disorders (*e.g.* Alzheimer's disease) and minocycline is currently being investigated for its therapeutic potential. However, it remains unclear whether this drug also has significant cognitive effects in healthy humans. We therefore used fMRI to test: 1) if minocycline can modulate healthy memory processes, and 2) whether such effects are principally mediated by MTL memory systems.

Methods: 20 health male subjects (mean age = 24.2) were recruited into a 2x2 repeated measures design; factor 1, minocycline vs placebo (100mg twice daily for 3 days prior to testing); factor 2, hippocampal vs non-hippocampal memory performance and BOLD activity. Two in scanner memory tasks were used; a virtual reality (VR) task constructed to simultaneously tap hippocampal- (boundary) and striatal- (landmark) based spatial navigation, and an object-in-place task designed to assess hippocampus independent item recognition and hippocampus dependant source-memory.

Results: Preliminary examination of the VR task behavioural data revealed that minocycline significantly enhanced the use of hippocampally mediated boundary based information without altering the utility of striatally mediated landmark based information. Complementary to this, behavioural data from the object-in-place task showed that minocycline enhances hippocampus dependent source memory but not hippocampus independent item recognition. Neuroimaging data will also be presented.

Conclusions: These preliminary findings suggest that minocycline may selectively exert beneficial effects on the MTL memory systems. Given that minocycline is thought to influence a variety of microglial mediated processes, the findings lend support to models of immune influences on memory function and suggest that minocycline may be an effective treatment for some neurodegenerative conditions.

Poster Ref: P2-D-060

Theme: D: Learning, Memory and Cognition

Interoceptive processing is disrupted in autistic spectrum conditions: implications for anxiety and emotion.

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Brighton Sussex Medical School

Body and brain are dynamically coupled: signals from the body can influence both emotional and cognitive processing. The anterior insula is a key region subserving the processing of both emotion and bodily awareness. Autistic Spectrum Conditions (ASC) are associated with deficits in identifying and processing emotion, and imaging studies also suggest aberrant insula activity and connectivity within these individuals. Reduced interoceptive accuracy in ASC individuals may thus underlie aspects of altered emotion processing. However, this hypothesized deficit in interoception appears not to accord with clinical observations suggesting heightened self-perceived body awareness in ASC individuals. Based upon our theoretical framework positing distinct interoceptive axes, we sought to reconcile these apparent discrepancies by measuring both objectively assessed interoceptive ability, quantified using performance during heartbeat detection tests (interoceptive accuracy) and individuals' subjective belief of their awareness of internal bodily sensations, assessed using a self-report questionnaire (interoceptive sensibility). As hypothesized, ASC was associated with both reduced interoceptive accuracy and heightened interoceptive sensibility, reflecting both an impaired ability to detection bodily sensations and an over-inflation of perceived interoceptive ability. The discrepancy between these two measures of interoception accounted for deficits in emotion sensitivity and also predicted heightened anxiety. Together these results suggest that an altered body-brain axis in ASC may contribute to difficulties in processing emotions and affective symptomatology.

Poster Ref: P2-D-061
Theme: D: Learning, Memory and Cognition

Spontaneous alternation Y-maze performance by female mice is significantly influenced by the sex of the experimenter.

Alex Harper, Gary Gilmour and Sophie Dix
Eli Lillly

Claims are frequently made that behavioural assays supportive of neuropsychiatric drug discovery efforts suffer from poor reliability, both within and between labs. Understanding sources of variance that impact results is key to understanding the true magnitude of the issue.

The spontaneous alternation Y-maze assay is frequently used as a first-line assay of spatial working memory and relies on the innate propensity of rodents to explore novel or less recently investigated environments. Rodents are presented an equal opportunity to select one of 3 walled arms while spontaneously exploring a Y-shaped maze. Normal exploration of the Y-maze requires intact hippocampal function (Naert *et al* 2013) and it is thought that animals may use distal spatial cues as landmarks as they traverse the maze. Basic levels of motor activity are reported as the distance moved, while a % alternation measure [number of arm entries/(number of alternations-2)] potentially provides some index of spatial working memory function here.

As a recent report demonstrated an effect of experimenter sex on baseline responses in mouse behavioural assays (Sorge *et al*, 2014), a retrospective analysis of data gathered from Y-maze experiments over several years was conducted to examine the generality of this effect. A significant interaction was found ($F_{1,1282}=11.4$, $p<0.001$) between experimenter and subject sex, where female mice moved significantly more when tested by male experimenters compared to females. No such interaction was observed with respect to % alternation in female mice, and no effects at all were observed in male mice. Thus, while cognitive performance per se was unaffected, hyperactivity seen in female mice exposed to the Y-maze by male experimenters may be caused by increased anxiety in response to the presence of a male experimenter. The study supports the conclusion of Sorge and colleagues that experimenter sex may influence behavioural performance, and further suggests that these effects may depend on the sex of the mouse as well. In general, the study points to the great potential for rationalising experimental variance that can be offered *via* thorough databasing of datasets.

Naert *et al.* (2013). Brain Research Bulletin. 94:71-81.
Sorge *et al*. (2014). Nature Methods 11: 629–632

Theme E: Sleep, Circadian and Neuroendocrine Mechanisms

Posters P2-E-001 to P2-E-017

Poster Ref: P2-E-001

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

Wakefulness is governed by GABA and histamine co-transmission.

Catriona Houston[1], Zhiwen Ye[1], Anna Zecharia[1], David Uygun[1], Ying Ma[1], Zhe Zhang[1], Alexei Vyssotski[2], Raquel Yustos[1], Nicholas Franks[1], Stephen Brickley[1], William Wisden[1] and Xiao Yu[1]

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Histaminergic neurons in the tuberomammilary nucleus (TMN) of the hypothalamus form a widely projecting, wake-active network that sustains arousal. Yet most histaminergic neurons contain GABA. Selective siRNA knockdown of the vesicular GABA transporter (vgat) in histaminergic neurons produced hyperactive mice with an exceptional amount of sustained wakefulness. Ablation of the vgat gene throughout the TMN further sharpened this mania-like phenotype. Optogenetic stimulation of “histaminergic” axonal projections in the caudate-putamen and layer IV of the neocortex evoked tonic (extrasynaptic) GABA-A receptor Cl- currents onto spiny stellate and pyramidal neurons. These currents were abolished in histaminergic neurons lacking vgat. Thus wake-active histaminergic neurons, in addition to releasing histamine, generate a paracrine GABA signal that will serve both as a brake on over-activation from histamine, but also increase the precision of cortical processing. The long-range of histamine-GABA axonal projections suggests that extrasynaptic inhibition will be coordinated over large cortical and striatal areas.

Poster Ref: P2-E-002

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

REM Sleep and other measures in rats receiving chronically administered paroxetine either daily or *via* continuous infusion.

Elaine Shanks[1], Nicola Hewes[1], Alexander Maxfield[1], David Bender[2], Andrew McCarthy[1], Keith Wafford[1] and Wesley Seidel[1]

[1]Lilly, Windlesham, [2]Lilly, Indianapolis, Indiana, USA

SSRIs produce an immediate suppression of REM sleep (REM), but its relation to the therapeutic response, which requires 2-3 weeks, remain unknown. To better understand dosing effects and REM suppression, we examined daily changes in sleep/wake parameters over a 2 week period during which paroxetine was given as a daily bolus or *via* continuous infusion.

Experiments were performed in accordance with the Animal (Scientific Procedures) Act 1986. Adult male Wistar rats (250-320g; n=39) were implanted with a telemeter i.p. and with a custom cranial implant. Animals were evaluated in the SCORE2004™ bioassay, which allows continual measurement and vigilance state scoring of electro-encephalogram (EEG) and electromyogram (EMG) (cranial implant), locomotor activity and body temperature (telemetry). Animals were kept under 12/12 light/dark cycle with food and drink ad libitum. Study 1: animals (n=24) were administered 5mg/kg paroxetine or 1ml/kg vehicle p.o. at lights on for 14 days followed by a 9 day washout period. Study 2: animals (n=15) underwent a further surgery to implant a programmable and refillable minipump (SMP-200, Primetech, Japan) s.c.. The minipump group (drug delivery i.p.) received 1ul/hr saline for 4 weeks (2 weeks post-operative and 2 weeks on study) followed by 14 days of paroxetine (30mg/ml at 5ul/hr) and a further 2 weeks of saline 5ul/hr.

In both studies, REM during the light phase was inhibited without tolerance throughout the 14 day treatment. In study 1, REM was unaltered during dark periods. A prominent REM rebound followed drug discontinuation. In study 2, REM was initially reduced during dark but returned to baseline levels between days 8-14 of paroxetine delivery. Upon drug discontinuation, REM was elevated only during the dark phase. In both studies, paroxetine increased sleep fragmentation and the circadian amplitude of body temperature whilst leaving NREM sleep relatively unchanged.

The minipump is a viable drug delivery device for chronic drug administration. REM inhibition and sleep fragmentation were observed in both studies. The response over time, however, reflected drug administration timing and the short half-life of paroxetine.

Poster Ref: P2-E-003

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

Dynamics of cortical neuronal activity during rapid eye movement sleep episodes in young and older mice.

Laura E. McKillop, Nanyi Cui, Simon P. Fisher and Vladyslav V. Vyazovskiy
University of Oxford

Sleep consists of two states – nonrapid eye movement (NREM) and REM sleep, of which NREM predominates. The role of the periodic excursions into REM sleep is unclear. It has been proposed that REM sleep plays a role in the regulation of hippocampal and/or cortical excitability and is an integral part of the process of sleep homeostasis. Evidence has shown ageing to be characterised by an increased sleep fragmentation, but it is unknown whether the intraepisodic dynamics of cortical activity, specifically during REM sleep, is also affected. The aim of this study was to investigate the cortical neuronal multiunit activity (MUA) within individual REM sleep episodes in young and older mice.

MUA was recorded from the primary motor cortex of young (92±17 days, n=4) and older (346±4 days, n=6) male C57BL/6J mice, using a 16 channel microwire array. Waking, NREM and REM sleep from the middle three hours of the light period (LD 12:12) were scored manually in 4-s epochs using cortical EEG and EMG. REM episodes that were artefact-free and >60 sec in duration were included in the analyses. The time course of MUA within each REM episode was calculated by subdividing each episode into six equal intervals.

MUA showed pronounced variability both between individual recording channels and within REM sleep episodes, although most recording channels showed an increase in overall firing rates (young animals: 11.7±8.0% increase, p=0.07; older animals: 14.9±4.0% increase, p=0.01, repeated measures ANOVA). In young mice (n=4, total channels=43), 10 channels showed an overall decrease in MUA, 4 remained stable and 29 channels increased by >5%. The corresponding values in older mice (n=6, channels=83) were 16, 9 and 58 channels, respectively. Although firing rates on average increased throughout REM sleep episodes, the maximal value was sometimes attained earlier in the episode, and was significantly different between ages (across all channels and animals, young: 4.0±0.1, older: 3.7±0.1, p=0.03, paired t-test).

In summary, the overall neuronal firing rates increased significantly across individual REM sleep episodes, irrespective of age. The results are consistent with the notion that REM sleep may be involved in the overall regulation of cortical excitability and sleep homeostasis.

Poster Ref: P2-E-004

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

A functionally distinct form of wake promotion is induced in rats by the mGluR5 potentiator LSN2814617.

Sally Loomis, Andrew McCarthy, Christopher Baxter, Daniel Kellet, Dale Edgar, Mark Tricklebank and Gary Gilmour

Eli Lilly

Background. Excessive Daytime Sleepiness is co-morbid with many neuropsychiatric conditions and there remains an unmet clinical need in this area. Little translational behavioural pharmacology has been conducted in this context, where effects of potential pro-vigilant compounds are assessed for their ability to restore functional capacity in the face of experimentally induced sleep loss. The aim of this work was to directly compare an mGlu5 potentiator, namely LSN2814617, to the known wake-promoting agents modafinil, caffeine and amphetamine on performance of a simple response latency task in the rat following biofeedback-induced sleep restriction.

Methods. Male Wistar rats were prepared for electroencephalographic (EEG) recording, and subject to 11 hours of sleep restriction using a biofeedback-induced cage turning protocol. A Simple Response Latency Task was used to behaviourally index sleep restriction and the effects of pro-vigilant compounds: amphetamine, caffeine, modafinil and LSN2814617.

Results. Sleep restriction resulted in a consistent, quantified loss of non-REM and REM sleep that impaired SRLT performance in a manner suggestive of progressive task disengagement. All compounds significantly increased EEG-defined wakefulness following sleep restriction for several hours following dosing. However, from a functional perspective their effects were quite disparate. Amphetamine treatment further decreased SRLT performance capacity, whereas the other three compounds decreased omissions and allowed animals to re-engage in the task. Both caffeine and modafinil also significantly increased premature responses during this period, an effect not observed for LSN2814617.

Conclusions. Simple response latency testing can reliably index the effects of sleep restriction in rats. Pro-vigilant pharmacologies were found to have differential effects on the ability to restore rat SRLT performance despite all having significant effects on EEG-defined wakefulness. The mGlu5 PAM LSN2814617 improved functional capacity of sleep-restricted animals, appearing qualitatively distinct from that of amphetamine, caffeine and modafinil.

Poster Ref: P2-E-005

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

Computational modelling of serotonin and orexin/hypocretin mediated GIRK and TRP-like currents.

Alok Joshi[1], T. Martin McGinnity[2,3], Girijesh Prasad[3] and KongFatt Wong-Lin[3]

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The brain's serotonin and orexin/hypocretin neuromodulatory systems are important for regulating cognition, mood and behaviour, and their dysfunctions are implicated in many mental and behavioural disorders. There is increasing evidence of direct and indirect interactions between the serotonin (5-HT) neurons in the dorsal raphe nucleus (DRN) and orexin/hypocretin (Ox/Hcrt) neurons in the lateral hypothalamus (LHA). To better understand the complex relationship between 5-HT and Ox/Hcrt and their combined modulatory functions, multiscale computational models with sufficient biological details of their interactions become necessary. In particular, we have previously identified and computationally modelled the DRN-LHA circuit and its dynamics [1].

In this work, we integrate various electrophysiological and pharmacological data to develop, for the first time, more biologically realistic computational models of 5-HT (1A) mediated G protein-activated inwardly rectifying potassium (GIRK) currents and Ox/Hcrt mediated transient receptor potential (TRP) like currents. We demonstrate how these currents can regulate 5-HT and Ox/Hcrt at the neuronal and circuit levels, including in the presence of pharmaceutical drugs. Our spiking neuronal circuit model also predicts 5-HT 1A agonist can enhance more synchronous periodic spiking activity in the network. Our computational modelling of 5-HT and Ox/Hcrt mediated currents sets the foundation for further in silico studies to investigate neuromodulatory systems interactions and systems pharmacology, and their effects on sleep and neuroendocrine mechanisms.

Reference

[1]. Jalewa, J., Joshi, A., McGinnity, T.M., Prasad, G., Wong-Lin, K. and Hölscher, C. (2014) Neural circuit interactions between the dorsal raphe nucleus and the lateral hypothalamus: An experimental and computational study. PLoS ONE, 9(2): e88003, 2014.

Poster Ref: P2-E-006

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

The role of BACE1 in hypothalamic leptin sensitivity.

Susan M. Jalicy[1], Paul J. Meakin[1], Yu-Ru Liu[2], Charlotte L. S. Bailey[2], J. Kim Dale[2] and Michael L. J. Ashford[1]

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Objectives: The β-site amyloid precursor protein-cleaving enzyme 1 (BACE1) is a key enzyme involved in the development of Alzheimer's disease (AD). Obesity and type 2 diabetes are risk factors for AD, which is also associated with impaired insulin sensitivity and glucose metabolism. BACE1-/- mice are protected against diet-induced obesity (DIO) and have improved glucose homeostasis and leptin sensitivity. Therefore the aim of this study was to determine whether central inhibition of BACE1 could mimic these effects and investigate the molecular mechanisms underpinning these outcomes.

Methods: The BACE1 inhibitor (BACEi, 10mg/kg), or vehicle (DMSO/PBS) was constantly infused into the lateral ventricle using an osmotic minipump connected with a brain infusion kit into DIO C57BL/6 mice. Body weight and food intake were measured daily for 4 weeks and glucose homeostasis assessed at the end of the study *via* intraperitoneal glucose and insulin tolerance tests. Immunohistochemistry (IHC) and fluorescent in-situ hybridization (FISH) techniques were used to investigate hypothalamic BACE1 expression. Data are expressed as mean ± standard error. Significance ($p \leq 0.05$) was determined by unpaired 2-tailed Student's t-test.

Results: Central administration of BACEi significantly reduced body weight (Control: 0.57± 1.4%; BACEi: -15.4 ± 2.8%; $p<0.001$) and improved glucose disposal during a glucose tolerance test (AUC: Control: 1357 ± 65.8; BACEi: 1020 ± 66.9; $p<0.01$), however insulin sensitivity and food intake was unaltered. IHC demonstrated BACE1 is present in distinct sub-populations of neurons, but not astrocytes, throughout the hypothalamus; and a proportion of these are GABAergic neurons in the arcuate nucleus (ARC). In the ARC, IHC and FISH showed BACE1 was partially co-localised with neuropeptide Y-, but not POMC-expressing neurons.

Conclusions: Central inhibition of BACE1 reduced body weight and improved glucose homeostasis in DIO mice. Further investigation of hypothalamic BACE1 expression, specifically defining neuronal subtypes, will help elucidate the mechanism(s) whereby BACE1 inhibition improves leptin sensitivity and alters energy metabolism. The knowledge from this research may provide a novel therapeutic strategy for the treatment of obesity/diabetes.

Poster Ref: P2-E-007

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

Ventral tegmental area 5-HT2C receptor activation reduces food reward.

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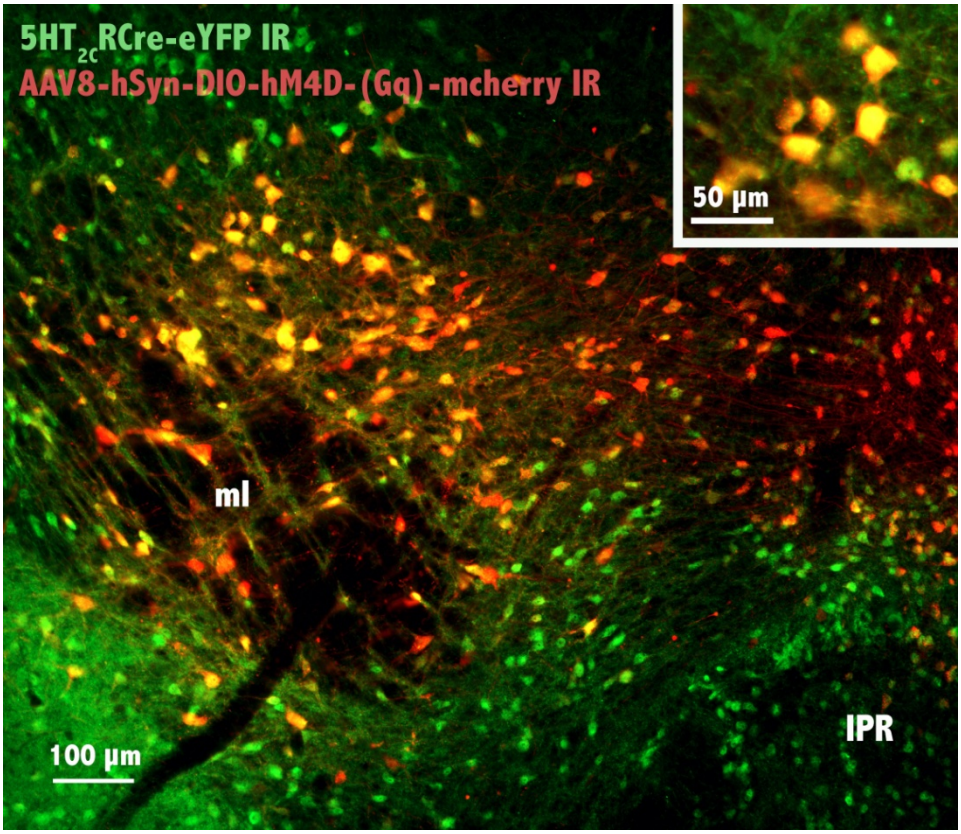
Rowett Institute of Nutrition and Health, University of Aberdeen

Dopamine (DA) release from the ventral tegmental area (VTA) is involved in several aspects of appetitive motivation and regulates the “rewarding” aspects of primary reinforcers such as food. The 5-hydroxytryptamine (5-HT) 2c receptor (5-HT2CR) is localised within the VTA and thereby may be a modulator of mesoaccumbens dopamine neurotransmission. Using a 5-HT2CR-Cre yellow fluorescent protein (YFP) reporter mouse line, we observed that 5-HT2CR colocalises with DA and γ-aminobutyric acid (GABA) VTA neurons. Using Designer Receptors Exclusively Activated by Designer Drug (DREADD) technology to activate 5-HT2CR neurons, we found that VTA 5-HT2CR neurons influence performance on a progressive ratio (PR) schedule. In the PR schedule, the ratio at which the subject stops responding, the breakpoint, is widely regarded as a measure of the incentive value of the reinforcer. Acute activation of VTA 5-HT2CR reduced the breakpoint. In addition, stimulation of VTA 5-HT2CR neurons suppressed feeding and locomotor activity in metabolic cage assessment. These results suggest 5-HT2CR is not solely involved in homeostatic feeding, but influences food reward by modulating the activity of DA neurons within the VTA.



Designer Receptors Exclusively Activated by Designer Drug (DREADD) injected into the ventral tegmental area (VTA) targets 5-HT2cR neurons. Representative VTA (bregma level: -3.28 mm) image of immunofluorescence (IF) for hMD4 (red) illustrating localisation in 5-HT2cR neurons (green) in 5-HT2c-cre::EYFP mice.

Poster Ref: P2-E-008

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

The effects of glucocorticoids on hippocampal network activity and interactions.

Alice Fodder, Matthew Jones and Stafford Lightman

Bristol University

Acute and chronic stress are well known to affect cognitive function. These effects are partially mediated through stimulation of the hypothalamic-pituitary-adrenal axis, leading to activation of mineralocorticoid (MR) and glucocorticoid (GR) receptors by glucocorticoids (corticosterone in rodents). These receptors are expressed in brain regions crucial for memory consolidation, including the hippocampus, prefrontal cortex (PFC) and amygdala. It is known that both the intensity and timing of a stressor relative to the stage in the memory process (encoding, consolidation and recall) will lead to differential effects on memory performance. However, the mechanisms underlying these effects are not yet fully understood.

Using *in vivo* multiple single neuron and local field potential (LFP) recordings coupled with glucocorticoid administration in behaving rats (n=3), we have investigated the effects of 0.3-3mgkg-1 i.p. doses of corticosterone on neuronal activity in the CA1 and CA3 regions of dorsal hippocampus. Corticosterone injections were interleaved between repeated exposures to a novel open field arena, allowing quantification of effects on both resting and waking (place cell) firing patterns. Glucocorticoids did not significantly change basic properties of ripples, high-frequency oscillations associated with memory consolidation. 0.3mgkg-1 of corticosterone led to a marked increase in the firing rates of CA1 putative pyramidal cells, which was then dampened by the higher 3mgkg-1 dose. Additionally, the higher dose of corticosterone injected during the consolidation period following exposure to a novel environment destabilised CA3 place cells, leading to global remapping ($p<0.05$ vs. vehicle controls). These findings reflect previous *in vitro* electrophysiological and behavioural studies, highlighting how different doses of glucocorticoids lead to altered excitability of the hippocampus with high doses impairing spatial memory consolidation.

As glucocorticoids have been implicated in altering the activity of other brain regions essential for mnemonic function, we are currently using simultaneous LFP recordings from CA1, PFC and basolateral amygdala to assess the changes in coherence between these brain structures following corticosteroid administration.

Poster Ref: P2-E-009

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

Effects of global brain state and specific behaviour on the activity of cortical neurons in freely moving mice.

Simon Fisher, Laura McKillop, Nanyi Cui and Vladyslav Vyazovskiy
University of Oxford

Global cortical neuronal firing rates are on average higher in activated brain states, such as waking and REM sleep compared with NREM sleep. The fluctuations in the activity of cortical neurons on the one hand may be driven in a top-down manner by an unspecific influence from subcortical neuromodulatory systems and on the other hand could emerge in a bottom-up fashion due to their involvement in network activity related to specific behaviours. To disentangle these possibilities we investigated cortical multi-unit neuronal activity (MUA) across a repertoire of spontaneous behavioural states. To our knowledge this is the first study of cortical MUA in freely-moving, non-head-fixed rodents during running-wheel (RW) activity. MUA was recorded from nine C57BL/6 mice (3-4 mths, n=4; 11-13 mths, n=5) using 16-channel microwire arrays implanted chronically in deep cortical layers of the primary motor cortex. Recordings started at least 2-3 weeks post-surgery. Vigilance states were defined based on cortical EEG and nuchal EMG signals. For each animal, representative episodes of waking, RW activity, NREM and REM sleep were selected during the dark period. Epochs of RW activity were subdivided into high and low-speed running based on the number of revolutions per second. At least 6 recording channels with robust MUA were included per animal (60 channels total, n=9 mice). Overall cortical firing rates decreased by 19.5±4.5% (mean, SEM) during high-speed running *vs*. non-running wakefulness. Across all animals, MUA in 38 recording channels (63%) was higher during non-running waking *vs*. running, while it was only lower in 16 channels (27%). Notably, in the same animal we often observed neuronal populations behaving in an opposite manner in relation to each other and running behaviour. In most cases, MUA was lower during NREM and REM sleep *vs*. waking. Our initial data indicates that this approach appears promising for "behavioural phenotyping" of individual neurons, to investigate their activity patterns during subsequent sleep. Our results raise an interesting possibility that global cortical states could be triggered and maintained not only by an unspecific bottom-up activation but also regulated at a local level by involvement of individual neurons in specific behaviours.

Poster Ref: P2-E-010

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

An *in vitro* non-image forming visual slice preparation.

Lydia Hanna, Michael Howarth and Timothy M. Brown

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In addition to supporting the detection and response to form and motion in the environment, a subset of the retinal output targets an interconnected network of retinorecipient nuclei controlling reflex responses to ambient illumination (the suprachiasmatic nucleus: SCN, intergeniculate leaflet: IGL and the pretectal olivary nucleus: PON). To better understand the functional organisation of this 'non-image forming' (NIF) visual system, here we set out to establish an *in vitro* preparation that retains connectivity between these anatomically dispersed nuclei.

A characteristic feature of NIF visual nuclei is that each receives substantial input from a subclass of intrinsically photosensitive melanopsin-expressing retinal ganglion cells (mRGCs). Since connections between the NIF nuclei are also known to follow the optic tract, here we employed x-gal histochemistry in melanopsin reporter mice (Opn4tauLacZ) to model the axonal trajectories linking these regions. Based on this modelling, we identified a slicing angle of 30^{o} off the coronal plane and a slice thickness of 600μm was required to preserve retinal projections and the majority of each nucleus intact. Multi-electrode array recordings from mouse brain slices prepared using these parameters reliably revealed the presence of glutamatergic excitatory responses to optic chiasm stimulation in all NIF nuclei, confirming that optic connections between these nuclei remain intact in our preparation. Moreover, we were able to identify the presence of GABAergic inhibitory responses in the SCN following electrical or optogenetic stimulation of the IGL, confirming the presence of a functional geniculohypothalamic tract (GHT). Finally, we confirmed that despite their relative thickness, these preparations remained viable for more than 24h *in vitro*, allowing us to record circadian oscillations in SCN neuronal firing rate.

In summary, we have established a useful new tool for probing the network organisation of the non-image forming visual system that will be especially useful for understanding the circuitry and neurochemical messengers regulating the circadian system.

Poster Ref: P2-E-011

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

Cessation of sleep-related bursting *via* differential modulation of K+ channel subtypes by phospholipase C in rat thalamocortical relay neurons.

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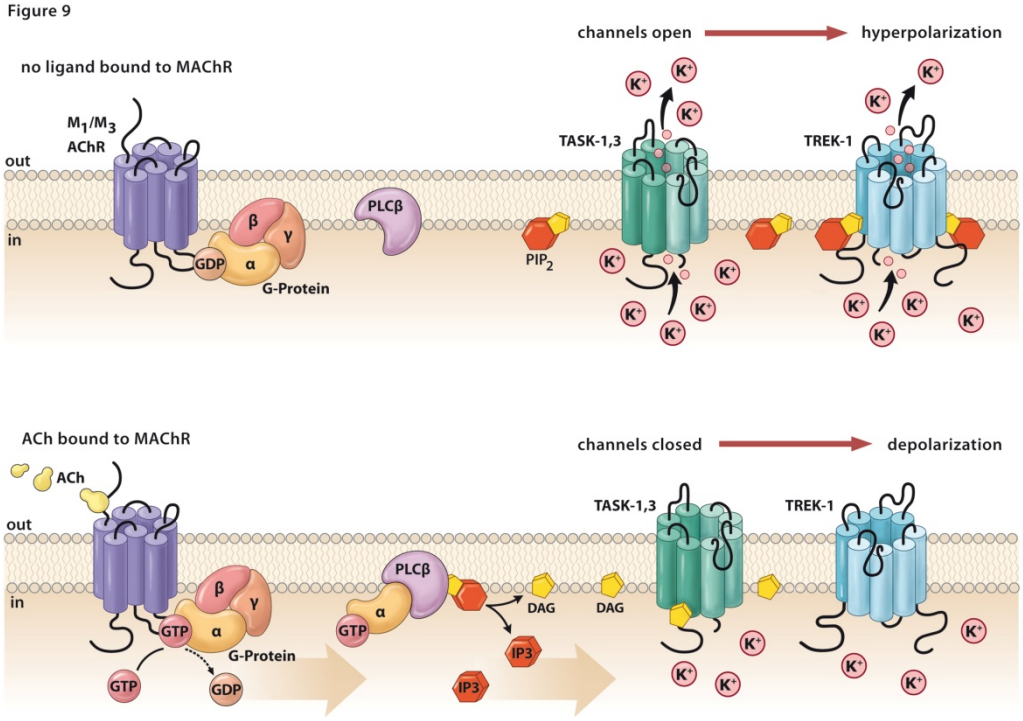
During the behavioural states of sleep and wakefulness, the thalamocortical (TC) system is characterized by two fundamentally different states of neuronal activity: tonic and burst firing. Two-pore domain potassium channels (K2P) influence the excitability and firing modes of TC neurons. Stimulation of muscarinic ACh receptors (MAChR) induces an inhibition of TASK and TREK channels *via* phospholipase C (PLCβ) stimulation and consequently a shift from burst to tonic firing. By using a whole cell patch-clamp approach, the contribution of the membrane bound second messenger molecules phosphatidylinositol 4, 5-bisphosphate (PIP2) and diacylglycerol (DAG) acting downstream of PLCβ was probed. The standing outward current (ISO) was used to monitor the current through TASK and TREK channels in TC neurons. By changing the intracellular PIP2 level in TC neurons, we here show that scavenging of PIP2 (by neomycin) results in an increased muscarinic effect on ISO whereas increased availability of PIP2 (included in the patch pipette; histone-based carrier) decreased muscarinic signalling. The degree of muscarinic inhibition specifically depends on phosphatidylinositol phosphate (PIP) and PIP2 but no other phospholipids (phosphatidic acid, PA; phosphatidylserine, PS). The use of specific blockers revealed that PIP2 is targeting TREK but not TASK channels. Furthermore, we demonstrate that the inhibition of TASK channels is induced by application of the DAG analogue 1-oleoyl-2-acetyl-sn-glycerol (OAG). Under current clamp conditions the activation of MAChR and PLCβ as well as the application of OAG resulted in membrane depolarization, while PIP2 application *via* histone carrier induced a hyperpolarization. These results demonstrate a differential role of PIP2 and DAG in K2P channel modulation in native neurons which allows a fine tuned inhibition of TREK (*via* PIP2 depletion) and TASK (*via* DAG) channels following MAChR stimulation.

Figure 9



Proposed modulation pathway of TASK and TREK channels in TC neurons. Binding of ACh to AChR activates Gαq proteins. PLCβ-stimulation results in PIP2 cleavage and DAG production. Unbinding of PIP2 and binding of DAG leads to the closure of TREK and TASK channels, respectively. Consequently the membrane potential depolarizes which is the prerequisite for the switch from burst to tonic firing.

Poster Ref: P2-E-012

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

The mammalian circadian clock uses colour to estimate time of day.

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University of Manchester

Although the daily solar cycle is the dominant environmental signal regulating mammalian circadian timing, our understanding of how specific features of the light environment contribute to photoentrainment is incomplete. In particular, the extent to which changes in the spectral composition of ambient illumination could provide important timing cues remains unknown. Here we investigated this possibility using a combination of computational modelling, electrophysiological recordings and behavioural assays of circadian entrainment in mice.

Firstly, *via* modelling based on an extensive set of environmental spectral irradiance measurements, we show that the relative spectral composition of environmental light is more predictive of the solar angles around twilight than global measures of irradiance. Using *in vivo* electrophysiological recordings, we next identify a subset (~20%) of SCN neurons exhibiting the spectrally-opponent responses required to extract this information. Importantly, using visual stimuli designed to recreate various stages of twilight for the mouse visual system, we show that the firing rates of these spectrally-opponent SCN cells reliably track solar angles around twilight (a property that is deficient in non-opponent SCN cells). Finally, using in and ex vivo monitoring of photoentrainment to simulated twilight, we show that chromatic signals detected by cone photoreceptors significantly influence circadian phase, allowing mice to appropriately time their activity to the middle of the night. Together, these findings reveal a new sensory mechanism for estimating time of day.

Poster Ref: P2-E-013

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

Oxytocin is not required for 5-HT2CR agonist appetite suppression.

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Obesity is a primary healthcare challenge of the 21st century. A 5-hydroxytriptamine (5-HT; serotonin) type 2C receptor (5-HT2CR) agonist was recently approved for obesity treatment in the United States of America. However, the mechanisms through which 5-HT2CR agonists communicate therapeutic effects have not been fully elucidated. A primary pathway through which 5-HT2CR agonists reduce food intake is *via* activation of melanocortin circuits signaling through the melanocortin 4 receptor (MC4R). The neurochemical phenotype of MC4R expressing neurons underlying 5-HT2CR agonist appetite suppression is not known. A principal site of MC4Rs influencing appetite is concentrated within paraventricular nucleus of the hypothalamus (PVH), a critical brain region for feeding regulation. Given that a subset of PVH MC4Rs is expressed on oxytocin (OT) neurons and 5-HT2R agonists induce oxytocin release, we hypothesized that MC4R-mediated oxytocin may be a necessary mechanism through which the therapeutic effect of 5-HT2CR agonists is achieved. To investigate this, we administered an anorectic concentration of a 5-HT2CR agonist meta-chlorophenylpiperazine (mCPP) and using c-fos immunohistochemistry, examined the activity of PVH OT neurons. We observed that appetite-suppressing concentrations of mCPP significantly increased the activity of PVH OT neurons. To examine whether activity at these neurons is required for mCPP hypophagia, we pretreated rats with an OT receptor antagonist and observed that blockade of OT signaling did not prevent mCPP anorexia. Given that this could be a dose-related event, we repeated this experiment in mice with ablated PVH OT neurons. Supporting the pharmacological study, OT deficiency did not influence mCPP appetite suppression, suggesting that OT neurons are not a required component of mCPP appetite suppression. These data reveal that OT is not a necessary mechanism through which 5-HT2C receptor agonists achieve their therapeutic effect on food intake.

Poster Ref: P2-E-014

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

Eye-specific inputs to the mammalian suprachiasmatic nucleus.

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University of Manchester

The mammalian brain 'clock', the suprachiasmatic nucleus (SCN), is responsible for synchronising physiology and behaviour with daily changes in the environment. This process is believed to rely on a quantitative assessment of total ambient illumination, provided by direct retinal projections to the SCN. The mouse SCN receives equal innervation from either retina, but it is unclear whether these eye-specific signals are integrated at the level of primary retinorecipient neurons or within the SCN network. Here, using *in vivo* multielectrode recordings from the SCN of anaesthetised mice, we show that the majority of SCN neurons (67%) receive input from only one eye, with similar numbers driven by either retina (ipsilateral-56%; contralateral-44%). While we find that binocular inputs to a subset of cells are important for rapid responses to changes in illumination, we find no evidence indicating that any SCN cells is capable of reporting the average light intensity across the whole visual field. Our data therefore indicate that individual SCN neurons act as local irradiance coders, and that photic integration must occur primarily at the level of the SCN network. Owing to this arrangement, overall light evoked SCN activity at equivalent total irradiance is substantially higher when binocular signals are equally matched. Our data therefore predict that circadian entrainment would be unexpectedly impaired by non-uniform illumination of either eye.

Poster Ref: P2-E-015

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

Sleepwalker - an open source matlab toolbox for the translational analysis of sleep neurophysiology

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Current analyses of sleep electrophysiology data typically rely on manual scoring of characteristic oscillations and sleep stages. Although it is widely accepted that even expert scoring of sleep data can introduce considerable variability, no standardised method for the automatic detection of sleep events has been yet been developed. Moreover, analysis methods differ between human and rodent labs, which complicates the direct comparison of rodent and human data in translational research approaches.

Here we present a set of functions developed for the Matlab Environment (The Mathworks, Natick, MA) that allow detection and detailed analysis of slow, spindle and ripple events during non-rapid eye movement (NREM) sleep in rodent LFP and human EEG recordings. The algorithms use a power based threshold-detection method to create a set of candidate events which will then be tested to comply with a set of feature boundaries to ensure high selectivity for specific events. These boundaries are selected in a test run on a subset of data and the correct detection of events is checked manually. Once criteria are set, event detection can be run in a fully automatic mode to deal with large data volumes. To speed up computations the functions can optionally be run in parallel (through the Matlab Parallel Computing Toolbox) on multi-core hardware. The functions are designed to be modular and flexible so that users can add their own custom detection algorithms if needed. The result of an analysis run is compiled in a summary figure giving a quick overview of distributions of detected event properties.

We have tested the algorithms on sample datasets of rat LFP, human EEG and human intracranial LFP data and describe a brief comparison of slow, spindle and ripple event properties in rodents and humans. In our analyses, some properties of rodent and human NREM oscillatory events are remarkably similar, which presents a unique opportunity for translational research to use highly conserved sleep oscillations as an indicator of intact function of cortical, thalamic and hippocampal circuits.

Poster Ref: P2-E-016

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

Untangling the clock: towards a network view of the *Drosophila* circadian system.

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Circadian timing mechanisms synchronise to daily cycles of light, temperature, and mechanical stimuli. The traditional view of this system places light as the dominant of these environmental cues (or Zeitgebers), acting *via* discrete pacemaker cells in the clock to coordinate behaviour.

Here we explore differential processing of sensory modalities in the *Drosophila* circadian system. Specifically, we ask what happens when Zeitgebers provide conflicting information. A combined behavioural and molecular analysis suggests that the circadian system integrates different types of sensory information to generate coordinated output. This challenges theories of light dominance and supports a growing view of the clock as a network of independent oscillatory subunits.

We go on to explore the roles of peripheral circadian oscillators (located outside the central clock) on behaviour. Preliminary data reveals a possible function of the period clock protein (PER) in mechanosensory organs, specifically in auditory mechanotransduction, which would highlight the intimate relation between clock gene expression and cellular function in the peripheral nervous system.

Poster Ref: P2-E-017

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

Modifying the SCN response to light using temporal modulation.

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Light regulates mammalian physiology and behaviour as it exerts effects on the master circadian oscillator, the suprachiasmatic nuclei (SCN). Electrophysiological recordings have shown that many SCN neurones are excited by ocular light exposure. The neuronal response to a simple light pulse has a clear form, comprising a sharp ON excitation that relaxes to a steady state firing, whose magnitude reflects irradiance of the step. The appearance of the ON response implies that, in addition to tracking background light intensity, these cells are disproportionately excited by abrupt increases in irradiance. This suggests that light therapies targeting the SCN could be made more efficient by including appropriate temporal modulations. We address this issue by comparing neuronal responses to fast (1s steps) and slow (0.01Hz sinusoids) changes in light to a sustained light of the same average irradiance.

All tests were conducted on Opn1mwR mice which have the human red cone opsin gene enabling the detection of input from different photoreceptors within the visual system. *In vivo* electrophysiological recordings were conducted on anaesthetised mice, using multielectrode arrays. Light was presented to the contralateral eye to stimulate neuronal responses within the SCN, which were recorded and analysed. Brains were then removed to confirm electrode placement.

We report that many SCN neurones are modulated by changes in irradiance, over a wide range of background light intensities. These effects are observed with gradual as well as abrupt changes and are positively correlated with the magnitude of the step. Most effective stimuli target all photoreceptive inputs, rather than increasing the irradiance of either rod/melanopsin or cone photoreception in isolation. Such information will contribute to successfully devising a number of specific light exposure paradigms which have a high chance of modulating circadian responses.

Theme F: Nervous System Disorders

Posters P2-F-001 to P2-F-058

Poster Ref: P2-F-001

Theme: F: Nervous System Disorders

Evaluating 2B3, a novel immunotherapy, in a preclinical amyloid pathology model of Alzheimer**'s disease.**

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Alzheimer's disease (AD) is the most common form of dementia and has no effective treatment. A major pathological hallmark of AD is the progressive build-up of β-amyloid (Aβ), which is cleaved from amyloid precursor protein (APP) by the enzymes β- and γ-secretase. We have developed a novel monoclonal antibody, 2B3, which binds to APP at the β-secretase cleavage site, inhibiting the production of Aβ by steric hindrance. The PDAPP model of amyloid pathology overexpresses an APP mutation found in human AD, and is reported to show an age-dependent rise in levels of Aβ and cognitive decline. The aims of this study are two-fold. 1) Characterise object recognition memory in the PDAPP model of AD at 6-8, 10-12 and 14-16 months of age to identify when age-dependent deficits become apparent and ascertain an age at which to test 2B3. 2) Assess whether 2B3 can alleviate any cognitive deficits observed in PDAPP mice following intracerebroventricular (ICV) administration. An age-dependent deficit in object-in-place memory was observed in PDAPP mice at 14-16 months of age compared to age-matched wild type (WT) mice, while object novelty memory remained unaffected across all ages examined. The deficit in object-in-place memory seen in the PDAPP mice with age has not been described previously. Following ICV administration of 2B3 for 14 days, PDAPP mice showed a significant improvement in object-in-place memory compared to vehicle treated PDAPP mice. Our findings with 2B3 provide *in vivo* evidence to show that inhibition of the metabolism of APP by β-secretase is an exciting target for immunotherapy in AD.

Poster Ref: P2-F-002

Theme: F: Nervous System Disorders

Investigating the utility of touchscreen cognitive testing in a regional cognitive disorders clinic.

Michael Lowe[1], Shuna Colville[2], Denise Cranley[2], Dawn Lyle[2], Francesca Cormack[3], Jenny Barnett[3] and Suvankar Pal[2]

[1]University of Edinburgh Medical School, [2]Anne Rowling Regenerative Neurology Clinic, University of Edinburgh, [3]Cambridge Cognition, Cambridge

Background: Dementia represents a major global public health challenge. There is an urgent need for improved sensitive and specific cognitive tests to facilitate early and accurate diagnosis.

Aim: To investigate the utility of touchscreen based Cantab neuropsychology tests in the diagnosis and differential diagnosis of dementia in patients presenting to an early onset cognitive disorders clinic.

Methods: 101 consecutive patients (60.5y ±7.90y, 59.4% male, 40.6% female) with an undifferentiated range of cognitive symptoms were evaluated. Clinical diagnoses (Alzheimer's disease (AD, n=33), frontotemporal dementia (FTD, n=17), subjective memory impairment (SMI, n=16), and other dementia syndromes (including vascular dementia and dementia with Lewy Bodies, n=35) were made according to consensus criteria following structured history, examination, and ancillary tests (MRI brain, HMPAO-SPECT and CSF analysis). Patients were assessed using a touchscreen based Cantab neuropsychology battery. Cognitive domains evaluated were episodic memory (EM), working memory (WM), attention (AT), executive function (EF) and processing speed (PS). Performance was adjusted for age, education and gender based on a large normative dataset.

Results: EM, WM and EF were significantly impaired in all patients with dementia compared to patients with SMI. Patients with AD demonstrated impairment in all cognitive domains other than PS compared to patients presenting with SMI, and performed worse on tests of WM compared to patients with FTD. Generally, touchscreen testing was efficient (<20 minutes), although 21% of patients (with prominent visuospatial or motor impairment) were unable to complete assessments.

Conclusions: Touchscreen cognitive testing using Cantab neuropsychology tests detected deficits in multiple cognitive domains in patients presenting with all forms of dementia. Furthermore, comparison between groups demonstrates differences in the profiles of patients with AD compared to SMI. The battery was easy to administer, advantageous in patients with expressive speech disturbance but difficult for patients with visuospatial or motor impairment. Further studies with larger numbers of patients are required to investigate the utility in differentiation of AD and FTD.

Poster Ref: P2-F-003

Theme: F: Nervous System Disorders

Cognition in neuromyelitis optica: a systematic review & narrative analysis.

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Background: Neuromyelitis Optica (NMO) is an antibody-mediated central nervous system disorder characterised by optic neuritis and longitudinally extensive transverse myelitis. Whilst there are clinical similarities with multiple sclerosis (MS), it is widely considered that cognition is spared. Recently, case series have reported neuropsychological deficits in attention, information processing speed and memory in patients with NMO.

Objectives: This systematic review aims to evaluate cognitive performance in NMO and compare profiles with healthy controls and patients with MS.

Methods: A systematic review and narrative analysis of studies investigating cognition in NMO was performed searching Ovid Medline, Ovid Embase and PubMed using the Medical Subject Headings Neuromyelitis Optica, Cognition, Cognitive Disorders and Memory from 2004-2014.

Results: 6 studies fulfilled inclusion criteria, including 129 patients with NMO, 61 patients with MS, and 158 healthy controls. Neuropsychological tests used included the Brief Repeatable Battery of Neuropsychological Tests and the California Verbal Learning Test. Patients were matched for age and education and disease course and severity. Significant cognitive impairment was demonstrated in patients with NMO in all studies compared with healthy controls. The profile of deficit varied but memory impairment was uniformly identified. Impaired information processing speed and attention were identified in most studies, and impaired executive function, learning and verbal fluency in individual studies. There was no significant difference between NMO and MS reported.

Conclusion: Patients with NMO demonstrate significant cognitive impairment similar in severity to patients with MS. Cognitive symptoms are potentially functionally impairing, impact on quality of life, and are generally under-recognised and incompletely evaluated. These results suggest patients with NMO should be counselled about the risk of cognitive impairment and symptoms screened for during clinical assessments. Larger studies are warranted with a more versatile range of cognitive tests, and controlling for common confounders to better inform clinical practice aiming to assess if clinical phenotype or MRI changes predict cognitive deficits.

Poster Ref: P2-F-004

Theme: F: Nervous System Disorders

Neuromodulation of tinnitus *via* spectral energy contrasts in tailor-made notched music.

Alwina Stein[1], Alva Engell[1], Pia Lau[1], Robert Wunderlich[1], Markus Junghoefer[1], Andreas Wollbrink[1], Maximilian Bruchmann[1], Claudia Rudack[2] and Christo Pantev[1]

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Introduction: Tinnitus is an auditory phantom sensation and seems to be caused by reduced inhibition in the auditory cortex. The perception itself as well as its neural correlates can be reduced by inducing inhibition onto the over-activated neurons coding the tinnitus frequency, also known as inhibition-induced plasticity. This can be achieved by listening to tailor-made notched music with the notch centered at the individual tinnitus frequency (tailor-made notched music, TMNM). A different degree of spectral energy contrasts in sounds can modify the degree of lateral inhibition in masking paradigms. Here we investigated, if also inhibition-induced plasticity can be enhanced by introducing increased spectral energy contrasts (ISEC) in TMNM.

Methods: Eighteen participants with chronic tonal tinnitus listened to either classical or ISEC-TMNM for three hours on three consecutive days. The music was filtered in both groups with a notch filter centered at the individual tinnitus frequency. In the ISEC-TMNM group, the edge frequency bands around the notch were additionally amplified by 20 dB. Subjectively perceived tinnitus loudness was rated on a visual analog scale before and after music exposure. Additionally, participants were stimulated with either a reference tone of 500 Hz or a test tone representing the individual tinnitus frequency in the magnetoencephalograph.

Results: Subjective tinnitus loudness was significantly reduced after TMNM exposure, though TMNM type did not influence the loudness ratings. Tinnitus related neural activity in the N1m time window was reduced after TMNM exposure in temporal, parietal and frontal cortical regions, also known as the tinnitus network. The ISEC-TMNM group revealed even enhanced inhibition-induced plasticity in a temporal and a frontal cortical area.

Conclusion: Overall, inhibition of tinnitus related neural activity could be strengthened in people affected with tinnitus by increasing spectral energy contrast in TMNM. These new insights confirm the concept of inhibition-induced plasticity *via* TMNM and possibly provide a new treatment strategy for chronic tonal tinnitus.

Poster Ref: P2-F-005

Theme: F: Nervous System Disorders

Investigating the contribution of axonal torpedo formation to Purkinje cell vulnerability in patients with mitochondrial disease.

Jonathan Phillips, John Grady, Robert Lightowlers, Doug Turnbull and Nichola Lax

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The central nervous system (CNS) is highly dependent on mitochondria for ATP generation, *via* oxidative phosphorylation (OXPHOS). In patients with mitochondrial disease, due to genetic defects in either mitochondrial or nuclear DNA, disruption of OXPHOS is frequently observed and associated with compromised ATP generation. Since mitochondrial function is crucial for the CNS, patients with mitochondrial disease frequently develop neurological deficits associated with degenerative changes occurring in the brain. The cerebellum is commonly affected in mitochondrial disease and clinically this manifests as ataxia. It is not known why the cerebellum is particularly vulnerable, however previous neuropathological studies identify axonal torpedoes as a prominent degenerative feature. These appear as fusiform swellings of axonal segments located proximally to Purkinje cells and contain a high concentration of disorganised neurofilaments. Our understanding of the mechanisms leading to formation of torpedoes and the consequence on Purkinje cell function remain undetermined.

In this study, formalin-fixed cerebellum sections were obtained from patients harbouring genetic defects causing mitochondrial disease (n=10) and control subjects (n=13).This reveals an increased axonal torpedo density in patients compared to controls. Using a quadruple immunofluorescent assay, we have quantified expression of key OXPHOS proteins (including complex I 19kDa and complex IV subunit IV) in mitochondrial populations within Purkinje cells, torpedoes and axons. CI 19kDa expression was observed to be reduced in Purkinje cell bodies, axons and axonal torpedoes of mtDNA patients compared to controls. In addition the level of myelination is altered by axonal torpedo formation with the majority of axonal torpedoes being unmyelinated.

In this study, we show increased Purkinje cell axonal swellings are present in patients with mitochondrial disease. Our data shows that these are not associated with respiratory chain deficiency however the formation of axonal torpedoes disrupts the myelin sheath. Mitochondrial dysfunction combined with axonal torpedo formation is likely to increase the burden on neurons.

Poster Ref: P2-F-006

Theme: F: Nervous System Disorders

Disruption of cortico-accumbal synchrony in the sub-chronic phencyclidine model of schizophrenia in rats.

Aman Asif-Malik, Andrew M J Young and Todor V Gerdjikov

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Sub-chronic treatment with the NMDA antagonist phencyclidine (PCP) produces behavioural abnormalities in rodents which are considered a reliable pharmacological model of neurocognitive deficits in schizophrenia. Alterations in prefrontal neuronal firing after acute PCP administration have been observed, however enduring changes in the cortico-accumbal circuit after sub-chronic PCP treatment have not been studied. To address this we have recorded unit responses in the medial prefrontal cortex (mPFC) and nucleus accumbens (NAc) in freely moving rats pre-treated with sub-chronic PCP (2mg/kg twice daily for 7 days). We found that this regimen, which produced deficits in novel-object recognition (NOR), decreased firing rates in the NAc in response to novelty compared to controls. Prefrontal synchrony and synchrony between the mPFC and the NAc were also reduced in PCP pre-treated animals. Consistent with the role of NAc and mPFC in motivation and attention, these deficits may drive schizophrenia-like cognitive deficits observed after sub-chronic NMDA antagonist treatment in rats.

Poster Ref: P2-F-007

Theme: F: Nervous System Disorders

The study of age-dependent changes in hippocampal network transmission in the triple transgenic A Alzheimer**'s disease mouse model.**

Seong Jeon

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Alzheimer's disease (AD) is a neurodegenerative condition and form of dementia. Initial cognitive impairment in early AD is due to dysfunction of the hippocampal complex and intracellular β-amyloid (Aβ) is believed to play a major role. To study effect of Aβ over-expression on hippocampal function, the triple-transgenic Alzheimer's disease mouse model (3xTgAD) was used and compared to aged-matched background strain controls. Multi-site recording was performed *in vitro* on horizontal brain slices using perforated multi-electrode arrays (pMEAs). This allowed the whole hippocampus to be assessed simultaneously for the generation and propagation of spontaneous activity and for the spread locally-evoked synaptic events following electrical stimulation. Input output (I/O) curves and a range of paired-pulse intervals (0.02-1s) were used to measure stimulus-response relationships and short-term plasticity, respectively. The initial area of interest was the CA3 region adjacent to the fimbria, which was evaluated in three different age ranges (3-4, 6-7 and 8-9 months old).

This study revealed that, in both control and 3xTgAD mice, there was an age-dependent decrease in both I/O curve slope and paired-pulse facilitation following local cell body layer stimulation in the CA3 region. These results suggested that there was a general decrease in the CA3 associational pathway during aging in both 3xTgAD and control mice. Furthermore, the 3xTgAD mice showed age-dependent changes in excitability in this associational pathway not seen in the controls. High-intensity 2.5V paired-pulse stimulation induced epileptiform activity (EA) in slices from 3xTgAD but not the control mice at 3-4 months. This activity was initiated in the region bordering CA1 and was then propagated both towards CA1 subiculum, and the proximal CA3 region and dentate gyrus. This suggested that by 3-4 months, chronic exposed to Aβ had induced a hyperexcitable network state in the CA3 region of these mice. However, this phenomenon was age-dependent, so that at 6-7 months, the ability to induce this EA was reduced to 50% of the 3xTgAD mice tested, and lost completely at 8-9 months old. These observations suggest that aging and/or a long-term adaptive mechanism then occlude this initial CA3 region hyperexcitablity.

Poster Ref: P2-F-008
Theme: F: Nervous System Disorders

Hippocampal inhibitory circuit dysfunction in AlzheimerAlzheimer**'s disease pathology.**

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Epileptiform activity is prevalent in Alzheimer's disease (AD) patients, and also detectable in animal models of disease pathology (Amatniek *et al.* 2006, Palop *et al.* 2007, Palop and Mucke, 2009 Vossel *et al.* 2013). Furthermore, antiepileptic drugs are known to improve cognitive impairments in both patients with mild cognitive impairment and animal models of AD (Bakker *et al.* 2012, Sanchez *et al.* 2012). However, the underlying cause of seizure development in AD is undetermined.

Recent papers report alterations in inhibitory neurons in brain tissue from patients (Schwab *et al.*, 2012) and animal models of AD (Baglietto-Vargas *et al.* 2010, Takahashi *et al.* 2010, Verret et al 2012). Early dysfunction of the inhibitory network could contribute to the enhanced network excitability seen in AD. However, the impact of AD pathology on particular forms of inhibition (Klausberger and Somogyi, 2008) remains to be determined.
Our project aims to elucidate inhibitory circuit changes that occur early in the progression of AD pathology, and to understand the impact of these changes on network function.

Hippocampal CA1 is one of the first regions affected in AD (West *et al.*, 1994). Using whole cell patch clamp recording from acute hippocampal slices, we are assessing the changes to different forms of functional inhibition in the CA1 in a mouse model of AD at ages preceding beta-amyloid deposition (J20, Mucke *et al.*, 2000). In parallel experiments we assay *in vivo* network changes by recording EEG from the CA1 of the hippocampus in freely moving mice using an implanted electrode coupled to a subcutaneous wireless transmitter (Open source instruments, Chang *et al.* 2011).
In vivo EEG recordings reveal hippocampal seizures. However, Schaffer collateral recruitment of feedforward inhibition appears unaffected in J20 mice, when comparing IPSC amplitudes to controls, both at 1 month (61.32 ± 19.94pA n=4 vs. 40.57 ± 6.918pA n=10 respectively, p=0.23) and 3-4 months (56.44 ± 15.36pA n=6 vs. 60.58 ± 16.24pA n=10, p=0.87). Studies of alternative pathways are in progress.

These data will provide mechanistic insight into epileptogenesis in AD pathology and so may reveal targets for therapeutic interventions

Poster Ref: P2-F-009

Theme: F: Nervous System Disorders

Lysosomal downregulation of M2 muscarinic acetylcholine receptors.

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Muscarinic Acetylcholine receptors (mAchR) are critical regulators of both the autonomic and central nervous systems. The M2 mAchR in particular has critical roles in regulating both heart rate and also synaptic transmission within the CNS, and the loss of M2 AchRs has been implicated in both learning and memory and also the progression of Alzheimers Disease, however the mechanism by which M2 AchRs undergo downregulation remains understood. These important receptors are members of the G-protein-coupled receptor (GPCR) superfamily, responsible for the regulation of a number of physiological processes. GPCR function is regulated by a complicated trafficking process involving phosphorylation, arrestin interaction, endocytosis and then either recycling to the plasma membrane or proteolytic degradation (1). Despite a great deal being known about the early trafficking processes of the M2, little is known about what determines the postendocytic fate (2). Using a combination of immunofluorescent microscopy and Western Blotting we demonstrate that following stimulation with carbachol the M2 AchR undergoes rapid proteolysis within the lysosome following sequential trafficking through Rab5 and Rab7 positive compartments. We further demonstrate that this process is dependent on HRS and functional ESCRT machinery, indicating the requirement for ubiquitination in this process. This is the first time that the processes responsible for M2 AchR have been identified and may lead to the identification of novel target for therapeutic intervention.

1. Hislop and von Zastrow (2011) Traffic 12 p137-48
2. Reiner and Nathanson (2012) Handb Exp Pharmacol 208 p61-78

Poster Ref: P2-F-010

Theme: F: Nervous System Disorders

Mitochondrial organisation is regulated in part by ER-shaping proteins, the loss of which is the leading cause of the neurodegenerative disorder hereditary spastic paraplegia.

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Hereditary spastic paraplegias (HSPs) are a group of neurodegenerative disorders characterised by degeneration of the upper motor neurons in the corticospinal tract leading to muscle weakness and spasticity. There are currently no treatments to cure or even slow the course of these diseases. The most common cause of HSP is mutations in genes encoding endoplasmic reticulum (ER)-shaping proteins, loss of which causes disruption in axonal smooth ER organisation and neurodegenerative phenotypes. However, the mechanism by which neuronal degeneration occurs in HSP is not known.

We have generated cell and animal models of HSP by knocking down the genes encoding the ER-shaping proteins Reticulon and ADP-ribosylation factor-like 6 interacting protein 1 (ARL6IP1) in HeLa cells and the fruit fly *Drosophila melanogaster*. We have found that neuronal loss of either Rtnl1 or Arl6IP1 (*Drosophila* orthologs of mammalian RTN1-4 and ARL6IP1 genes respectively) results in progressive degenerative phenotypes in both larvae and adult flies. We imaged GFP tagged-mitochondrial within the motor neurons of Rtnl1 and Arl6IP1 RNAi larvae and detected a reduction in mitochondrial load in long motor neurons compared to controls. Interestingly, we also reveal that these findings translate to a human cell model as loss of Reticulons and ARL6IP1 from HeLa cells also results in disrupted mitochondrial organisation and decreased mitochondrial localisation in the periphery of knockdown versus control cells.

These findings point to a conserved role for ER-shaping proteins in coordinating mitochondrial organisation and suggest a novel mechanism by which loss of ER-shaping proteins may underpin neurodegeneration in human disease.

Poster Ref: P2-F-011

Theme: F: Nervous System Disorders

Different requirements for the VCP co-factors Npl4 and Ufd1 in neuronal function in *Drosophila melanogaster*.

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Neuronal aggregates containing ubiquitinated and disease-causing mutant proteins, most frequently the RNA-binding protein TDP-43, are a common feature of amyotrophic lateral sclerosis (ALS). This suggests that the ubiquitin-proteasome system (UPS), the primary system responsible for the maintenance of protein turnover, is a critical factor in the pathogenesis of ALS. Supporting this, mutations in several genes encoding proteins which function in the UPS have been shown to cause ALS, most notably valosin-containing protein (VCP). Recent reports have proposed increasing the function of VCP as a therapeutic strategy to treat ALS. However, VCP has multifaceted roles in various cellular pathways, with the action of VCP determined by its association with different protein co-factors, e.g. VCP-Npl4-Ufd1 complexes function in UPS while VCP-p37 functions in golgi/ER biogenesis. Therefore, therapeutic strategies aimed at stimulating the UPS should likely be targeted to the VCP-Npl4-Ufd1 complex, which is poorly understood in neurons.

We have characterised the roles of Npl4 and Ufd1 in neurons *in vivo* by targeted gene knockdown in the fruit fly *Drosophila melanogaster*. Neuronal-specific knockdown of Npl4, but not Ufd1, results in widespread neurodevelopmental disruption. Specifically, analysis of motor neurons in Npl4 RNAi larvae reveals disrupted microtubule organisation within axon fibers and at the neuromuscular junction (NMJ), and fewer mitochondria are detected within the axons of Npl4 RNAi neurons. Furthermore, neuronal loss of Npl4, and to a lesser extent Ufd1, causes progressive degeneration with adult flies displaying reduced survival (Npl4 RNAi) and locomotion (Npl4 and Ufd1 RNAi) compared to controls.

To explore how neuronal dysfunction caused by loss of Npl4 or Ufd1 may relate to ALS, we investigated how loss of these genes modified TBPH (*Drosophila* ortholog of TDP-43) expression in neurons. We identified increased cytoplasmic mislocalisation of TBPH in Npl4 RNAi neurons, consistent with the hypothesis that defects in UPS may underpin the pathogenic processes that lead to neurodegeneration in ALS. We have therefore generated a novel *in vivo* model in which to investigate the mechanism(s) by which UPS dysfunction contributes to ALS-associated neurodegeneration.

Poster Ref: P2-F-012

Theme: F: Nervous System Disorders

Glycosylation of PrPC is a key factor in determining TSE transmission between species.

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The risk of transmission of transmissible spongiform encephalopathies (TSE) between different species has been notoriously unpredictable because the mechanisms of transmission are not fully understood. A transmission barrier between species often prevents infection of a new host with a TSE agent. Nonetheless, some TSE agents are able to cross this barrier and infect new species with devastating consequences. The host PrPC misfolds during disease pathogenesis and has a major role in controlling the transmission of agents between species, but sequence compatibility between host and agent PrPC does not fully explain host susceptibility. PrPC is post-translationally modified by the addition of glycan moieties which have an important role in the infectious process. Here we show *in vivo* that glycosylation of the host PrPC has a significant impact on the transmission of TSE between different host species.

We infected mice in which the first (N180T), second (N196T) or both (N180T and N196T) N-glycan attachment sites are disrupted with two human agents (sCJDMM2 and vCJD) and one hamster strain (263K). The absence of glycosylation at both or the first PrPC glycosylation site in the host results in almost complete resistance to disease. Absence of the second site of N-glycan has a dramatic effect on the barrier to transmission between host species, facilitating the transmission of sCJDMM2 to a host normally resistant to this agent. These results demonstrate that glycosylation of host PrPC can dramatically alter cross species transmission and is a key factor in determining the transmission efficiency of TSEs between different species.

The findings and conclusions in this article have not been formally disseminated by the Food and Drug Administration and should not be construed to represent any Administration determination or policy.

Poster Ref: P2-F-013

Theme: F: Nervous System Disorders

Action of a novel Kv3 channel modulator on primary auditory cortical oscillations *in vitro*.

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Tinnitus is a chronic condition that affects c.10% of adults. Aberrant cortical network synchronisation has been associated with tinnitus in human studies, with alterations in gamma (γ) and delta (δ) frequency oscillations noted. A modulator of the Kv3 family of potassium channels (AUT00063) is currently in development for the treatment of tinnitus. Kv3 channels are highly expressed in the central auditory system and this expression can be modulated by noise exposure. Kv3 channels are highly expressed by parvalbumin-positive (PV+) cortical inhibitory interneurons that are critical for the generation of γ frequency oscillations. We therefore examined the impact of the pharmacological modulation of Kv3 channels by AUT00063 on network function in the primary auditory cortex, *in vitro*.

Persistent γ (30-60Hz) and δ oscillations (1-4Hz) induced by kainate (400nM) were recorded from rodent primary auditory cortical slices, before and after application of AUT00063. No significant effects were observed with 1μM AUT00063; whereas a significant reduction in peak amplitude and area was observed at 3 and 10μM AUT00063. At 20 and 30μM, an increase was observed in both peak amplitude and area power of γ oscillations, that was significant at the higher concentration. In addition, AUT3 significantly altered δ activity. Whilst low concentrations of the drug had no effect, concentrations >10μM significantly increased the peak amplitude and power of neocortical δ oscillations.

These results confirm that AUT00063 can modulate gamma and delta frequency oscillations in the auditory cortex of normal hearing animals, *in vitro*, consistent with the role of Kv3 channels in regulating the firing of PV+ interneurons that are thought to underpin cortical network synchronisation. These data suggest that Kv3 channel modulation may have potential for therapeutic benefits in patients with tinnitus; however, it will be important to evaluate effects of AUT00063 in slices obtained from animals that have undergone acoustic over-exposure and exhibit a behavioural phenotype associated with tinnitus.

Poster Ref: P2-F-014

Theme: F: Nervous System Disorders

Glutamate receptor mediated modulation of dopamine release in nucleus accumbens is not affected by sub-chronic phencyclidine pretreatment, in rat brain slices *in vitro*.

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The glutamate theory of schizophrenia derives from reports that non-competitive NMDA receptor antagonists such as phencyclidine (PCP) induce the full spectrum of symptoms (positive, negative, cognitive) in normal people, and enhance these symptoms in schizophrenia sufferers. Changes in dopamine function associated with schizophrenia may be secondary to glutamate dysregulation, and mediated through glutamate-dopamine interactions in limbic regions, including nucleus accumbens (NAc). In animal models, twice daily treatment with PCP for 5 days ('sub-chronic' treatment), causes behavioural changes, which mimic aspects of schizophrenia, and which endure for many months after the end of drug administration. It also causes enduring changes in dopamine function in NAc and frontal cortex. This implies that the drug has caused conformational changes in neural function and/or organisation, which may be similar to those seen in schizophrenia, an understanding of which may elucidate changes occurring in the brain leading to schizophrenia. We have used fast cyclic voltammetry in rat brain slices *in vitro*, to measure the effects of local activation of glutamate receptors on basal and potassium (K)-stimulated dopamine release from NAc shell, and to investigate whether the effects of the drugs are changed by sub-chronic pretreatment with PCP. Application of NMDA caused an increase in basal dopamine levels, but no consistent change in K-stimulated dopamine levels. Activation of metabotropic (mGluR) glutamate receptors, using the mGluR2 agonist, LY379268, or the mGluR5 positive allosteric modulator, CDPPB, did not affect basal levels of dopamine, but attenuated K-stimulated levels of dopamine. Animals which had received sub-chronic pretreatment with PCP showed the expected behavioural deficits in the novel object recognition task, and, in tissue taken from these animals, K-stimulated dopamine release was enhanced. However, there was no effect of pretreatment on the NMDA- or mGluR- mediated changes in basal or K-stimulated dopamine release provoked by either drug. It is therefore unlikely that the effects of PCP pretreatment on schizophrenia-like behaviours are mediated by local modulation of accumbal dopamine release by these classes of glutamate receptor.

Poster Ref: P2-F-015

Theme: F: Nervous System Disorders

A direct mechanism for the MCT Ketogenic diet in seizure control.

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The focus of our research is the mode of action of the medium chain triglyceride (MCT) ketogenic diet, a carbohydrate-restricted diet rich in medium chain triglycerides that is used to treat children with drug resistant epilepsy. Whilst the mechanism of action is commonly assumed to be based on ketogenesis, it has recently been shown that decanoic acid, one of the major components of the diet, directly reduces seizures *in vitro* independently of ketones (Chang *et al.* 2013).

Our recent data suggests an effect of decanoic acid on post synaptic excitatory neurotransmission. We thus employed the *Xenopus laevis* expression system, where the AMPA-type glutamate receptor subunits 1 and 2 (GluA1/2) or 2 and 3 (GluA2/3) genes were expressed to produce heterologous receptor proteins in the oocytes. We then measured AMPA receptor generated currents in the presence of glutamate and decanoic acid using the two-electrode voltage clamp method. We find that decanoic acid directly inhibits AMPA receptors (Fig. 1), with an IC50 of 0.52mM. Furthermore, we have been able to demonstrate that this inhibition is specific to decanoic acid, since octanoic acid, the other major component of the MCT ketogenic diet displays much weaker inhibitory activity (IC50 = 3.8mM). To further characterize this inhibitory effect, we show decanoic acid-dependent AMPA receptor inhibition is noncompetitive to glutamate, subunit-specific (with a stronger inhibition on GluA2/3 receptors), and use-dependent (with a stronger inhibition in depolarized cells). We are also developing new, more potent antiepileptic drugs based on this mechanism. We have been able to identify novel compounds based on the structure of these medium chain fatty acids that show 20-fold increased potency compared to decanoic acid.

Our data suggests that the MCT ketogenic diet may act directly to inhibit AMPA receptors by decanoic acid in the treatment of drug resistant epilepsy.

This work is funded by Vitaflo Ltd.

Reference:

Chang P, Terbach N, Plant N, Chen PE, Walker MC, Williams RSB (2013), Seizure control by ketogenic diet-associated medium chain fatty acids. Neuropharmacology; 69: 105-114.

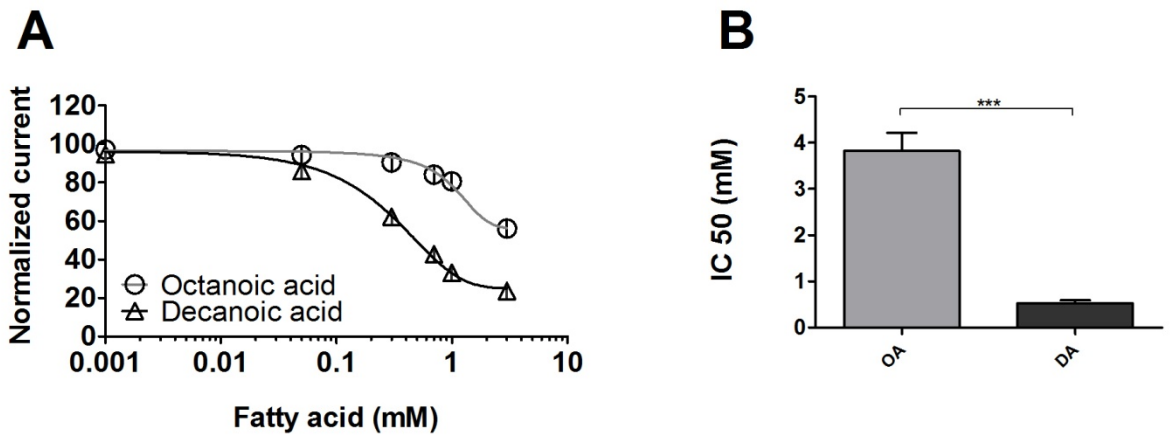

Figure 1. Dose response curve of inhibition of AMPA receptor generated currentsby decanoic acid and octanoic acid measured in *Xenopus laevis* opocytes using a two-electron voltage clamp (A). Comparison of IC50s of decanoic acid (DA) and octanoic acid (OA), (B).

Poster Ref: P2-F-016

Theme: F: Nervous System Disorders

Electrophysiological characterisation of neurons located within the Bed nucleus of the stria terminalis (BNST) in a novel model of tauopathy.

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Alzheimer's disease (AD) is a neurodegenerative condition which affects more than 500,000 individuals in the UK, of whom 88% will also suffer from neuropsychiatric symptoms. The bed nucleus of the stria terminalis (BNST) is a limbic forebrain structure which links the higher cognitive centres such as the hippocampus and prefrontal cortex with centres associated with neuroendocrine and autonomic systems such as the hypothalamus. Dysregulation of neuroendocrine control (potentially mediated by BNST dysfunction) has been reported in animal models of AD (Hebda-Bauer *et al.*, 2013). In order to characterise the role of the BNST in AD, we used whole-cell recording techniques to examine the intrinsic electrophysiological properties of BNST neurons in a novel mouse model of tauopathy (created in the Hanger lab) that express truncated human tau (TG male mice aged 14-18 months). These recordings were compared to similar recordings made from age-matched wildtype (WT) littermate control mice.

Whilst many intrinsic properties of BNST neurons (*e.g.* resting membrane potential and input resistance) were unaffected by the truncated tau expression, there were alterations in the action potential waveform (AP zenith: WT 16 ± 4 mV, TG 29 ± 4 mV, unpaired t-test, p = 0.02; peak maximum rate of rise: WT 185 ± 16 V/s, 262 ± 27 V/s, unpaired t-test, p = 0.02). Furthermore, the likelihood of generating post-hyperpolarisation rebound spikes was reduced in TG neurons (WT: 10/28 cells; TG: 3/21 cells, chi squared p = 4.24 e-5). WT cells which generated an afterhyperpolarization following a single action potential also exhibited rebound spikes (6/7 cells) whereas this relationship was abolished in the TG cells (1/7 cells, chi squared p = 2.3 e-10).

These data suggest that BNST neurons in this tauopathy model would respond aberrantly to phasic synaptic inputs. Therefore, it is possible that dysfunction within this pathway could be a contributing factor to the non-cognitive deficits observed in Alzheimer's patients.

Hebda-Bauer *et al.* (2013) 3xTg-AD mice exhibit an activated central stress axis during early-stage pathology. Journal of Alzheimer's disease, 33(2):407–22.

Poster Ref: P2-F-017

Theme: F: Nervous System Disorders

Structure based design and characterisation of small molecule human ABAD inhibitors as therapeutics in AlzheimerAlzheimer**'s disease.**

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Background: The mitochondrial enzyme, amyloid binding alcohol dehydrogenase (ABAD), has been shown to mediate the cytotoxic effects of Amyloid-β within the Alzheimer's diseased brain. Mutational studies have shown that ABAD must be catalytically active for cytotoxicity to be observed and therefore the direct inhibition of ABAD may offer a novel therapeutic strategy to treat the disease.

In 2006, Xie *et al.* identified benzothiazole urea analogues capable of perturbing the ABAD- Aβ interaction. We hypothesised that the capability of these analogues to disrupt the interaction may infer the ability to bind to ABAD, which in turn may inhibit ABAD activity. We have subsequently generated a further series of benzothiazole urea derivatives and assessed their ability to inhibit ABAD, identifying two inhibitors (article in press). Using SAR analysis we have designed further analogue series aiming for elevated potency and more desirable pharmacokinetic properties. Cell based studies have been used to further assess the therapeutic potential of these compounds.

Methods: Enzyme kinetic studies were performed using a spectrophotometer to measure the change in NADH absorbance (340 nm) over time as the substrate is reduced. Based upon these findings structural activity relationships were determined and further analogue series synthesised by our collaborators at University Hradec Kralove (Czech Republic). Cell based de-selection assays were used to verify the inhibitory nature, the cell permeability and cytotoxicity of these compounds.

Results: Enzyme kinetic studies yielded relative IC50¬ values in the low μM range for several analogue series. Subsequent cell based assays have assessed mitochondrial activity, cell permeability and their toxic nature. Structure based activity relationships have identified key moieties required for inhibition of the ABAD enzyme.

Conclusion: In conclusion we have characterised several potent inhibitors of the ABAD enzyme using recombinant enzyme extract and cell based studies. Based upon these preliminary findings we hypothesis that these compounds may have therapeutic potential in the treatment of Alzheimer's disease.

Poster Ref: P2-F-018

Theme: F: Nervous System Disorders

Differential vulnerability of motor neurons in mouse models of spinal muscular atrophy.

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Spinal Muscular Atrophy (SMA) is a neuromuscular disorder manifesting as muscle weakness and corresponding loss of lower motor neurons from the spinal cord. This disease is caused by mutations and deletions within the SMN1 gene. Although the best characterized role for this protein is in pre-mRNA splicing, it is unknown whether defects in splicing are the cause of pathology. Despite the ubiquitous expression of Smn, lower motor neurons appear to be primary targets in SMA, with degeneration of neuromuscular junctions representing an early and significant event in pathogenesis. Furthermore, not all motor units appear equally affected. Work from both mouse models and human patients has revealed that whilst there is a high degree of denervation in some muscles, others remain innervated even at late stages of disease. This is exemplified in the Smn2B/- mouse model of SMA in which there is a high degree of neuromuscular junction loss in the abdominal muscle groups, whilst those innervating the cranial muscles remain intact at disease end stage. We have recently performed a transcriptional screen on these differentially vulnerable motor neurons at a pre-symptomatic time point. In this project we will validate the changes which were identified in our transcriptional screen. This will be done both at the RNA and protein level. Changes will be validated using two different mouse models of SMA as well as patient cell lines. We will also investigate whether inhibition of identified pathways can have a beneficial effect on the phenotype of a mouse model of SMA.

Poster Ref: P2-F-019

Theme: F: Nervous System Disorders

The pattern of [11C]-Pittsburgh Compound-B binding in the brains of adults with Down's Syndrome.

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Introduction: Adults with Down's syndrome (DS) invariably develop beta-amyloid (Aβ) pathology indistinguishable from sporadic Alzheimer's disease (AD). Due to the trisomy 21 and triplication of APP, DS presents as a natural model of Aβ over-production. Studies in DS are highly complementary to those in autosomal-dominant AD in understanding the role of Aβ. This study characterises the sequence of Aβ accumulation in DS brains, which has implications for disease staging *in vivo* and monitoring response to treatment.

Methods: As part of a large cross-sectional investigation of AD in people with DS, forty-nine adults with DS underwent [11C]PIB-PET, with structural, diffusion weighted and functional MRI, and neuropsychological assessment. PIB images, a modified Brodmann atlas and FIRST subcortical maps were warped to a template, created from T1-images with ANTs, for quantification of regional non-displaceable binding potential. No participant without binding in the striatum had binding elsewhere and the distribution of striatal binding was bimodal with clear groups of negative and positive. The number of positive regions in PIB-positive group formed the basis for the accumulation model.

Results: Nine stages of PIB binding were identified: (1) striatum, (2) dorsal prefrontal and anterior cingulate cortex, (3) ventral prefrontal cortex and areas of the parietal lobe, (4) lateral temporal cortex and the rest of the parietal lobe, (5) sensory and motor areas, (6) associative visual and pre-motor cortex, and the rest of the temporal lobe, (7) occipital lobe, (8) thalamus and the medial temporal lobe, (9) amygdala. None of the participants were PIB positive in the hippocampus.

Conclusion: Aβ follows a pattern of accumulation measurable *in vivo* in DS. Evidence supports the initial involvement of the striatum as previously reported for DS and autosomal-dominant AD. In DS, the first cortical area affected by Aβ is the prefrontal cortex, followed by parietal, then temporal areas and, at the very late stages, occipital cortex. This progression model has the potential to inform future anti-amyloid primary prevention trials.

Poster Ref: P2-F-020

Theme: F: Nervous System Disorders

A multinutrient preparation developed for neurodegenerative disease enhances functional outcome following spinal cord injury.

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Spinal cord injury (SCI) leads to major neurological impairment, associated with significant tissue loss. Endogenous repair processes occur following SCI, but they are limited. Recent clinical trials in Alzheimer's disease have demonstrated the efficacy of Fortasyn® Connect (FC), a specific multinutrient combination that was designed to compensate for the loss of neuronal membranes and synapses in dementia patients, and that contains docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), choline, uridine monophosphate, phospholipids, folate, vitamins B6, B12, C, E and selenium. We tested if this multinutrient combination countered the tissue destruction occurring after SCI and supported regenerative processes, improving the neurological outcome. Adult rats received an injury induced by cord compression at thoracic level, and immediately after SCI they were fed daily with a control diet or a diet supplemented with different doses of the specific FC multinutrient combination (low dose FC, medium dose FC, or high dose FC) for 4 or 9 weeks. At 4 weeks, only 50% of rats that were fed the control diet were able to plantar place their paws, and only 2 rats had recovered gait coordination. In contrast, 6 out of 7 rats fed the diet with the high dose of FC had recovered a coordinated gait. Five of them showed a normal position of the paws and full recovery of toe clearance, and 2 of them showed a gait that was undistinguishable from that of uninjured rats. The BBB score was 17.1 ± 1.6 in this group, in comparison with the BBB score of 8.8 ± 1.3 in rats fed the control diet. This was accompanied by significant protection of oligodendrocytes and myelin in the injured tissue, a decreased microglial neuroinflammatory response, and an increase in pre- and postsynaptic markers. The medium dose of FC that did not show efficacy after 4 weeks of treatment led to improved motor score, increased neuronal and oligodendrocyte survival, decreased microglial activation, and better axonal preservation after 9 weeks of supplementation. These results suggest that a diet supplemented with this specific multinutrient combination has marked therapeutic potential in SCI.

Poster Ref: P2-F-021

Theme: F: Nervous System Disorders

Exploring the microvasculature of patients with mitochondrial disease.

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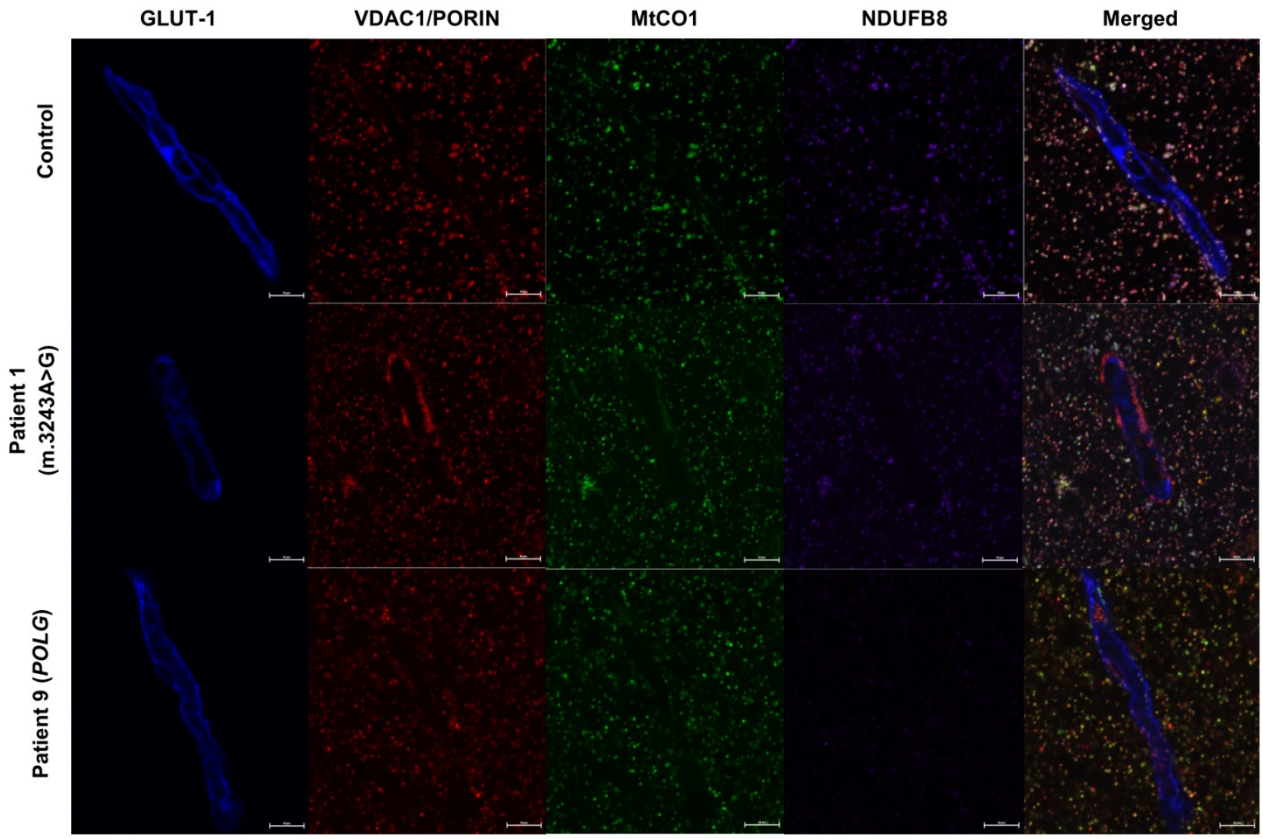
Introduction: Mitochondrial disease is the name given to a group of highly heterogenic genetic disorders. It emerges due to either primary or secondary mitochondrial DNA (mtDNA) mutations and is associated with deficits to the mitochondrial energy production system known as the oxidative phosphorylation system (OXPHOS). When the OXPHOS is malfunctional, all eukaryotic cells that contain mitochondria are short in energy (ATP) supply leaving highly energetic demanding tissues like the heart, brain and muscle severely affected.

Amongst the wide spectrum of neurological impairments are stroke-like episodes, which are a prominent feature of (but not restricted) to patients with the m.3243A>G point mutation associated with MELAS. Recent neuropathological investigations were demonstrative of COX-deficient smooth muscle and endothelial cells in patients with m.3243A>G and m.8344A>G point mutations and recessive POLG mutations. Moreover, increased mitochondrial presence within and thinning of both vascular layers was noticed.

Aims: Smooth muscle, endothelial cells and pericytes are key in controlling vascular tone and are therefore very important in providing neurons with oxygen and nutrients. We aim to examine respiratory chain protein expression in smooth muscle and endothelial cell layers and further assess pericyte morphology.

Methodology: A quantitative quadruple immunofluorescence technique was employed to measure complex I and IV protein expression (NDUFB8 and mtCO1) in the microvascular environment of the cerebellum and occipital cortex from 12 patients with mitochondrial disease and 10 age-matched controls.

Results: Preliminary data suggest a significant reduction of complex I accompanied by a milder decrease in complex IV protein expression in the endothelial and smooth muscle layers of patients with mitochondrial disease (Figure 1).
Discussion: Studying the microvascular environment of patients with mitochondrial disease is likely to help unravel the mechanisms that cause stroke-like episodes in these patients and further shed light to how these are linked to neuronal death and degeneration.



Quadruple immunofluorescence of cerebellar small vessels. GLUT-1 is used to detect endothelial cells. VDAC1 is a mitochondrial mass marker while NDUFB8 and MtCO1 proteins are employed to detect complex I and IV deficiency respectively. Control endothelial cells demonstrate colocalisation of VDAC1, NDUFB8 and MtCO1, while patients have decreased complex I and IV expression. Scale bar: 10μm

Poster Ref: P2-F-022

Theme: F: Nervous System Disorders

Brain-specific hBACE1 knock-in induces peripheral diabetes *via* abnormal hypothalamic function and loss of hepatic control.

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University of Aberdeen

Neuronal β-secretase 1 (BACE1) is associated with Alzheimer's disease (AD) due to its role in amyloid production *via* amyloid precursor protein (APP) cleavage. However, growing evidence suggests that BACE1 contributes to metabolic regulation and diabetic conditions, with BACE1 deletion protecting from high fat diet-induced obesity and diabetes *via* improved glycaemic control and insulin sensitivity.

We here investigated whether neuronal human BACE1 expression induces changes in central and/or peripheral glucose homeostasis, using a brain-specific human BACE1 knock-in mouse (PLB4). Male transgenic and wild type (WT) mice were assessed at 5 & 8 months for metabolic parameters, gene and protein expression related to insulin signalling as well as markers of endoplasmic reticulum (ER) stress. Despite a leaner phenotype (~-20% cf. WT), PLB4 mice were hyperglycaemic (>8mM) and glucose intolerant at 5 and 8 months of age cf. WT. Hyperinsulinaemia was only detected in the younger age group (~3ng/ml *vs.* ~0.8ng/ml in WT). Increased concentrations of gastric inhibitory polypeptide (GIP) were found in plasma of PLB4 mice, a likely response to hyperglycaemia and effectively leading to reduced body mass. Brain tissue displayed alterations in insulin sensitivity, *i.e.* elevated whole-brain expression of PTP1B, RBP4, rpS6 and marked increase in hypothalamic genes linked with obesity (POMC, MC4R) as well as ER stress markers (CHOP). These central alterations paired with elevated blood glucose and early hyperinsulinaemia promoted impairments in hepatic insulin sensitivity (~1.5-fold increase in PTP1B and RBP4), fatty liver phenotype (elevated triglyceride content and ApoE expression) and impaired glucose absorption in muscle (~10-fold increase in rpS6), but not in adipose tissue. Our results suggest that low expression of neuronal hBACE1 leads to major systemic abnormalities, similar to those observed in dietary diabetes models. The prominent elevation of hypothalamic peptide hormones and ER stress markers, together with whole-brain changes in insulin sensitivity, explain the diabetic profile of PLB4 mice. Importantly, our model confirms the major regulatory function of neuronal BACE1 in metabolic regulation and identifies BACE1 as a novel therapeutic target for AD and diabetes.

Poster Ref: P2-F-023

Theme: F: Nervous System Disorders

Effects of wild-type human tau overexpression on plaque-associated pathological changes in a novel model of Alzheimer's disease.

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Alzheimer's disease is characterized by the presence of aggregates of amyloid beta (Aβ) in senile plaques and tau in neurofibrillary tangles, as well as marked neuron and synapse loss in affected areas. Of these pathological changes, synapse loss correlates most strongly with the progressive cognitive decline in Alzheimer's. Synapse loss occurs prominently around plaques due to accumulations of oligomeric Aβ. Recent evidence suggests that tau may also play a role in synapse loss but the interactions of Aβ and tau in synapse loss remain to be determined. In this study, we generated a novel transgenic mouse, the APP/PS1/hTau line, by crossing APP/PS1 mice, which develop plaques with hTau mice which overexpress wild-type human tau. This line was used to assess the contribution of wild type human tau to Alzheimer's pathology. When compared to the APP/PS1 line without human tau, the size of ThioS+ dense core plaques and the number of dystrophic neurites per plaque were both found to be increased by ~40%, and axon curvature around plaques increased by ~15%. Analysis by ELISA and western blotting show a trend towards an increase in the amount of soluble Aβ in synaptoneurosomes of APP/PS1/hTau mice compared to APP/PS1 mice. The role of human tau in synaptic degradation is being further examined using array tomography to examine the density of pre- and post-synaptic markers around plaques. Together, these results indicate that human tau exacerbates plaque-associated degeneration in a mouse model and supports the hypothesis that Aβ and tau act synergistically to cause damage to neurites and synapses around plaques.

Poster Ref: P2-F-024

Theme: F: Nervous System Disorders

Harnessing the regenerative properties of inflammation to develop novel strategies for paediatric brain repair in cerebral palsy.

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Cerebral palsy is a lifelong disorder characterized by severe motor deficits and is incurred perinatally by inflammation and hypoxia in the brain. This induces proliferation of oligodendrocyte progenitors yet prevents oligodendrocyte precursor cell survival and differentiation into myelinating oligodendrocytes, causing hypomyelination and impaired nerve function. Current treatments aiming to dampen initial brain injury or manage symptoms are only marginally effective, highlighting the need for therapies that promote myelin repair. Our previous work showed that during efficient myelin repair in the adult brain, microglia and circulation-derived macrophages undergo a switch in activation from a pro-inflammatory phenotype which drives oligodendrocyte progenitor proliferation, to a regenerative phenotype which drives oligodendrocyte precursor survival/ differentiation and myelin repair. We hypothesized that following perinatal brain injury, pro-inflammatory microglia/ macrophage phenotypes predominate over regenerative phenotypes to drive the abovementioned pathology. Our analysis of post-mortem human brain tissue of perinatal brain injury and *in vivo* experimental models of this injury demonstrated an imbalance of microglia/ macrophage activation towards the pro-inflammatory phenotype. We developed a novel ex vivo forebrain explant model of perinatal brain injury induced by LPS-mediated sensitization followed by hypoxia, characterized by oligodendrocyte progenitor proliferation, precursor cell death, lack of differentiation and myelination. This was associated with a high ratio of microglia with a pro-inflammatory vs regenerative phenotype. Oligodendrocyte differentiation and/or survival were rescued by supplementation with conditioned media from regenerative microglia or novel factors we identified to be secreted by these cells. Our findings demonstrate that perinatal brain injury modulates microglia/ macrophage activation towards a pro-inflammatory phenotype unable to support oligodendrocyte precursor differentiation and survival, which can be rescued by factors secreted from microglia with a regenerative phenotype. This work has identified microglia and their secreted products as novel therapeutic targets to drive myelin repair following perinatal brain injury.

Poster Ref: P2-F-025

Theme: F: Nervous System Disorders

Studying glia-neuronal interaction in C9ORF72 expansion mediated ALS using an induced pluripotent stem cell based *in vitro* model.

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Background: Accumulating experimental and human pathological evidence implicates non-cell autonomous mechanisms in the aetiopathogenesis of motor neurone disease. Recent advances in the genetics of ALS show that GGGGCC hexanucleotide repeat expansion on C9ORF72 is the most common genetic cause of ALS (1). Astrogliosis and glial pathology has long been described in ALS but until recently has been assumed to be secondary and / or reactive (2). Human stem cell technologies allows the *in vitro* study of cellular autonomy with a focus on astrocytes.

Methods: Following a well-established protocol (3), astrocytes were generated from both healthy control and GGGGCC repeat expansion carrying induced pluripotent stem cell (iPSC) lines. Cell identity was examined by immunostaining against astrocyte markers and cell function was examined by glutamate uptake and calcium imaging. Fluorescent *in situ* hybridisation (FISH) was conducted to detect (GGGGCC)n RNA foci in differentiated astrocytes.

Results: Highly enriched (>90%) functional astrocytes were generated from both control and C9ORF72 expansion carrying cell lines. (GGGGCC)n RNA foci were detected in mutant astrocytes but not control astrocytes. Evaluation of the influence of genotype on cell viability in isolated and co-culture with neurones under basal and stressor conditions is ongoing.

Discussion and Conclusion: Our work has established a platform to investigate the glial pathology and potential non-cell autonomous toxicity of astrocytes in C9ORF72 related ALS.

Poster Ref: P2-F-026

Theme: F: Nervous System Disorders

Evaluation of the efficacy of a Kv3 ion channel modulator in the acute ketamine-challenge model of psychosis using pharmacological challenge functional MRI.

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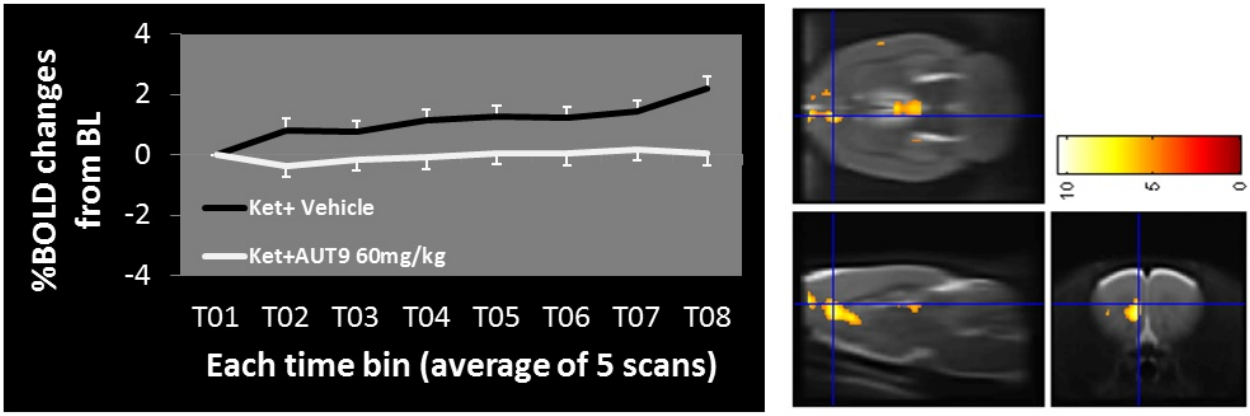
Introduction: Schizophrenia presents with both cognitive and social symptoms which can progress to functional deterioration and psychosis. The pathology of schizophrenia includes dysfunction of cortical networks with contribution from parvalbumin-positive (PV+) interneurons. Recently, brain Kv3 potassium channel mRNA & protein expression was found to be significantly reduced in untreated patients (1). Kv3 channels are primarily expressed by PV+ interneurons, thus reduced expression might contribute to their dysfunction and pharmacological modulation of the channels might be a means to treat disease. Here we examine the ability of AUT9, a novel selective modulator of Kv3.1 and Kv3.2 ion channels to prevent the characteristic alterations in brain function induced by low dose ketamine in rat.

Methods: We used an EPI sequence (TE/TR:15/3000ms) to acquire pharmacological-challenge fMRI (phMRI) images exploiting blood oxygenation level dependent (BOLD) contrast in a ketamine model of acute psychosis in male Sprague Dawley rats. Anaesthesia was induced with isofluorane (1.5%), maintained with α-chloralose (30-50mg/kg) and baseline scans were collected for ≥10min. Following an injection of AUT9 (60mg/kg, ip) or vehicle, animals were scanned for an additional 30min. They then received ketamine (30mg/kg, sc) and BOLD imaging was continued for 30min. All animals were monitored for vital signs (body temperature, respiratory rate, blood gasses, pH & glucose). phMRI scans were analysed using SPM8.

Results: Ketamine significantly changed BOLD signal in the prefrontal and parietal cortices, striatum, hippocampus and para-hippocampal regions as described previously (2). Pre-administration of AUT9 significantly reduced the ketamine mediated BOLD changes in cortices and striatum. AUT9 did not cause changes in BOLD signal on its own when compared to vehicle.

Conclusion: Using BOLD phMRI and an acute model of psychosis, we have shown that modulation of Kv3 channels might be a useful novel approach for the treatment of schizophrenia.

(1)-Yanagi, M., *et al.* Mol Psychiatry 19, 573 (2014)
(2)-Hodkinson, D.J., *et al.* Br J Med Med Res 2, 373 (2012).



Left: % BOLD signal changes after ketamine injection in striatum in vehicle treated group (black) vs AUT9 (60mg/kg) (grey). X-Axis: T01-T08 represent 8 time-bins (average of 5 scans, 205s). Y-Axis: % change in BOLD signal relative to baseline before administration of ketamine. Right: representative overlay images. The highlighted anatomical region shows striatum. Each study group n=6; $p<0.001$.

Poster Ref: P2-F-027

Theme: F: Nervous System Disorders

Acute exposure to NMDA receptor antibodies reduces gamma-frequency oscillation power in entorhinal cortex *in vitro*.

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Gamma (γ) frequency oscillations (30-80Hz) play an important role in cognitive processes and memory formation, and are disrupted in schizophrenia. NMDA receptor antagonists, which have been used to model schizophrenia in rodents, reduce γ-oscillation power and frequency *in vitro* in the entorhinal cortex (EC). We hypothesized that NMDA receptor antibodies (NMDAR-Abs) could similarly disrupt γ-oscillations in the EC. We examined the effects of acute and subacute exposure to NMDAR-Abs using an *in vitro* rat brain slice preparation.

For acute exposure, slices were perfused with purified patient or control serum immunoglobulin G (pIgG, cIgG) for one hour. Peak power and overall power in the γ-frequency range were reduced in slices exposed to pIgG (change in peak power: naïve slices 17.24±35.49% n=8, cIgG slices 20.67±30.65% n=13, pIgG slices 41.77±28.11% n=36, one-way ANOVA p=0.029; change in overall power: naïve slices 5.14±40.61%, cIgG slices 21.3±19.46%, pIgG slices 35.45±23.38%, p=0.009). However, frequency was unaffected (change -0.24±4.65% naïve slices, 3.36±4.48% cIgG slices, 5.05±12.14% pIgG slices, p=0.407). For subacute exposure, pIgG or cIgG were injected into the EC of young adult rats and the γ-oscillations studied ex vivo one to three days later. There were no differences in the baseline characteristics of γ-oscillations in the three groups (uninjected slices n=20, pIgG n=19, cIgG n=14); bath application of the NMDA antagonist D-AP5 (50μM) reduced oscillation frequency in all three groups (change: 8.41±7.55Hz naïve slices, 6.11±5.12Hz pIgG, 10.73±5.93Hz cIgG slices, two-way ANOVA $p<0.0001$), with no effect of IgG treatment.

The reduction in oscillation power after acute exposure to NMDAR-Abs suggests reduced inhibitory drive and thus less efficient recruitment to the γ-rhythm. The subacute exposure experiments did not confirm this, although this may relate to the small volumes injected, resulting in only a small area of IgG-bound neurons. Further studies are required to confirm the results and investigate the underlying mechanisms.

Poster Ref: P2-F-028

Theme: F: Nervous System Disorders

Reducing pathology in Alzheimer's disease through Angiotensin TaRgeting - the RADAR Trial.

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Background: Pre-clinical, observational and secondary analyses of clinical trials suggest Losartan and similar antihypertension drugs may be repositioned to treat Alzheimer's disease (AD). Losartan blocks angiotensin II signalling that may modulate mechanisms altered in AD including cholinergic transmission, inflammation, cerebral blood flow (CBF) plus amyloid and tau neuropathology. Losartan is one of several angiotensin II receptor blockers (ARBs) that are associated with lower incidence of AD compared to other anti-hypertension drugs. The protocol to test the therapeuticpotential of Losartan in treating both amyloid- and vascular-related pathology in AD is presented.

Methods: The RADAR trial is a multi-centre phase II, two arm, double-blind, placebo-controlled, randomised trial evaluating the effect of Losartan in patients diagnosed with AD. The primary outcome is change over 12 months in whole brain and ventricular volume by volumetric MRI (T1-MPRAGE). Secondary outcomes include: change in cognition, activities of daily living and quality of life (standard assessment battery); change in CBF (measured by arterial spin labelling); change in white matter hyperintensities (T2/FLAIR brain MRI); association between MRI measures and rate of cognitive decline; blood pressure changes and drug compliance and tolerability. The planned sample size of 228 participants will be recruited over 24 months in 7 sites nationally; recruitment commenced August 2014. Participants will be randomised to receive encapsulated 100mg of Losartan or placebo; taken once daily for 12 months. Prior to commencing the randomised phase, participants will need to complete a two-week open-label phase. Inclusion Criteria include: hypertensive and normotensive people with a diagnosis of probable AD according to NINCDS-ADRDA (supported by MRI/CT) aged ≥55 years; MMSE 18-28; modified Hachinski score of ≤5; and availability of an informant.

Discussion: Current treatments for AD (cholinesterase inhibitors) work as cognitive enhancers only. This trial will assess whether Losartan has a disease modifying effect on progression of AD. If successful, it will provide a cost-effective, safe treatment that is already widely used for hypertension.

Poster Ref: P2-F-029

Theme: F: Nervous System Disorders

Investigation of mechanisms underlying early metabolic adaptations in Alzheimer's disease.

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Background: Alzheimer's disease (AD) is the most common cause of dementia, accounting for more than 60% of cases. Importantly, and worryingly, there is presently no cure or means to slow disease progression. This represents a clear, unmet medical and socioeconomic need in light of the ageing population worldwide. Much of the current AD research focusses on analysing the brain once hallmark amyloid plaque and tau tangle pathologies have emerged. However, their appearance is extremely end stage and to date, any therapeutic interventions aimed at alleviating them have failed to halt symptom progression. It may therefore be more beneficial to look at earlier disturbances occurring in the brains of people who later develop AD. One such change is the reduced ability of the brain to utilise glucose; occurring potentially decades prior to brain atrophy and symptom presentation. Previous work from the Ashford lab suggests that the AD-associated protein β-site amyloid precursor protein cleaving enzyme 1 (BACE1) has a key role in whole body glucose homeostasis. With the knowledge that BACE1 protein and activity levels are increased in AD we therefore aimed to observe the effects of BACE1 overexpression on the use of primary neuronal substrates.

Methods: Studies were carried out in human neuroblastoma SH-SY5Y cells stably overexpressing BACE1. ^{14}C-labelled glucose oxidation, extracellular flux and enzyme activity assays were utilised to monitor metabolism in real-time.

Results: Chronically elevated BACE1 protein expression resulted in a significant reduction in glucose oxidation stemming from an increase in aerobic glycolysis (reflected by a significant reduction in oxygen consumption rate (OCR) and increase in extracellular acidification rate (ECAR)). These overall changes in fuel use appear to be driven by impairments in enzymes (pyruvate, isocitrate and alpha-ketoglutarate dehydrogenases) and pathways that control cellular oxidative metabolism.

Conclusions: In this cell model, overexpression of BACE1 phenocopies a number of the earliest detectable changes in the brain of people who later develop AD. Therefore, the enzymes observed to be impaired here may provide legitimate targets for therapeutic intervention against this devastating disease.

Poster Ref: P2-F-030

Theme: F: Nervous System Disorders

Inhibition of cyclin dependent kinase 5 associates with reduction in neuronal loss in an animal model of epilepsy

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Background: Approximately 30% of epilepsy patients will not respond to available antiepileptic drugs. The most common cause of pharmacoresistant epilepsy in adults is hippocampal sclerosis (HS), a condition characterized by segmental neuronal loss in the hippocampus which underlie both the epileptic seizures and the cognitive deficits seen in these patients.

We hypothesise that phosphorylation of the NMDA receptor by cyclin dependent kinase 5 (cdk5), contributes to NMDA receptor-mediated excitotoxic cell death in HS. We have previously demonstrated that there are changes in the levels and activity of cdk5 in human HS and now explore whether changes in cdk5 pathway might contribute to the neuronal loss seen in animal models of HS.

Methods: Pilocarpine-induced status epilepticus was induced in adult male Sprague-Dawley rats. Animals were sacrificed seven days after treatment with pilocarpine and then evaluated with biochemical analyses. Fluoro-jade C (FJ-C) was used to initially quantify neurodegeneration in animals treated with pilocarpine alone, pilocarpine and the cdk5 inhibitor roscovitine and pilocarpine and the NMDA receptor antagonist MK801. Qualitative and quantitative immunohistochemical staining and western blots were performed on the same cohorts.

Results: FJ-C staining showed that both roscovitine and MK801 significantly reduced neurodegeneration in studied areas of the hippocampus compared to animals treated with pilocarpine alone. Western blots show less neuronal loss in animals treated with roscovitine, although the result did not reach clinical significance.

Conclusions: Our results further indicate that cdk5 might contribute to neuronal loss in HS as inhibition of this pathway associates with less neuronal loss in animal models of HS. Given the intimate association between cdk5 and NMDA receptor in mediating hippocampal neuronal loss, administration of MK801 might also, of itself, alter cdk5 activity and the exact contribution of NMDA-receptor mediated excitotoxicity to neuronal loss in HS requires further delineation.

Future work: Planned studies include immunohistochemical and biochemical analysis of NMDA receptors in surgically-resected human HS and similar evaluation of NMDA receptor in animal models of HS treated with anti cdk5 inhibitors.

Poster Ref: P2-F-031

Theme: F: Nervous System Disorders

Coinfection with a neurotropic virus substantially alters pathological features of the neurodegenerative disease process.

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Viral infection has a controversial role in the process of neurodegeneration having been implicated in both precipitating and driving the disease process. We have taken a novel approach to assess the potential impact that a single subclinical acute neurotropic viral infection Semliki Forest virus (SFV A7(74)) can have on neurodegenerative disease progression. We utilise the Prion model ME7 as they display all of the core features of neurodegeneration with immune activation, disease associated protein deposition and neuronal loss. Interestingly, we observe that a single coinfection event with a neurotropic viral agent has the ability to alter multiple aspects of disease, such as; regional targeting, neuronal survival, inflammatory profile and biochemical properties of the misfolded prion protein.

Moreover, we find that different pathological features may be altered depending on the phase of the neurodegenerative process within which the challenge has occurred. These data outline the substantial and previously unreported impact that a single acute subclincal neurotropic viral challenge can have on the core features of the neurodegenerative process. This will have important consequences for identifying suitable therapeutic targets for the pathological processes of neurodegneration.

Poster Ref: P2-F-032

Theme: F: Nervous System Disorders

Parvalbumin-positive interneuron density in auditory and frontal cortices in a mouse model of 22q11.2 Deletion Syndrome.

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22q11.2 Deletion Syndrome (22q11DS) is a genetic syndrome that results from a 1.5-3Mb congenital multigene deletion on the long arm of chromosome 22. Approximately 25-30% of adults with 22q11DS develop schizophrenia during adolescence or adulthood. As one of the most significant known cytogenetic risk factors for schizophrenia, 22q11DS holds the potential to provide insight into neural systems abnormalities associated with schizophrenia. The Df1/+ mouse model of 22q11DS recapitulates many features of human 22q11DS and schizophrenia, including cognitive impairment and frequent otitis media, a middle ear disease that can cause conductive hearing loss. In other model systems, both hearing loss and schizophrenia risk factors have been shown to be associated with abnormalities in parvalbumin-positive (PV+) inhibitory interneuron circuitry in the cortex. However, the relationship between hearing loss, genetic risk of schizophrenia, and PV+ interneuron circuitry remains poorly understood. Here we explored this relationship by examining PV+ interneuron density in the auditory and frontal cortices of Df1/+ mice with and without conductive hearing loss. Previous work (Fuchs *et al.* 2013) has shown that approximately half of Df1/+ mice have conductive hearing loss due to otitis media; moreover, the hearing loss is frequently monaural. We tested for otitis media or hearing loss in both left and right ears of Df1/+ mice and their WT littermates, using tympanic membrane inspection and/or auditory brainstem response measurements. Then, we performed PV+ immunohistochemistry on coronal sections through the auditory and frontal cortices of the mice, and quantified PV+ interneuron density across cortical layers. Comparing results between Df1/+ and WT mice, we found significant reductions in PV+ interneuron density in Df1/+ mice, especially in cortical layers III to VI of the primary auditory cortex. However, among the Df1/+ mice, we also found a correlation between reduced PV+ interneuron density in the auditory cortex and hearing loss in the contralateral ear. The results suggest that genetic risk of schizophrenia and developmental hearing loss could interact to produce cumulative abnormalities in PV+ interneuron networks.

Poster Ref: P2-F-033

Theme: F: Nervous System Disorders

Recognition memory in the Tc1 mouse model of trisomy 21.

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The Tc1 mouse is a model of trisomy 21, which manifests as Down syndrome (DS) in humans. Previous work has suggested a specific deficit in short-term but not long-term recognition memory in Tc1 mice. Thus, Morice *et al.*, (2008) revealed impaired novelty detection following a short (10 min) but not long (24 hr) delay using an object recognition task. Tc1 mice were able to detect a novel cue only after a 24 hour delay between sample and test trial. Intriguingly, O'Doherty and colleagues (2005) used a similar object recognition procedure except that mice received two sample phases separated by 24 hours before a novelty test conducted shortly after the last sample trial. Despite the 24 hour interval between sample phases, Tc1 were impaired following a short delay. Given the theoretical importance of alerted short-term but not long-term memory in Tc1 mice, the present study was deigned to establish the effect of short and long-term retention intervals on object recognition memory in Tc1 mice. The results confirm and extend the observation that recognition memory in Tc1 mice is sensitive to the interval between the sample and test trial. In addition, the study aimed to ascertain the effects of the Tc1 mutation on spatial memory ability, by using an object in place task. The results indicate disparity in the deficits of the Tc1 mouse with regards to spatial recognition memory and object recognition memory.

Poster Ref: P2-F-034

Theme: F: Nervous System Disorders

GABAergic synaptic density in the hippocampal CA1 of a mouse model of Alzheimer's disease pathology.

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A growing number of reports suggest that seizures are part of the progression of Alzheimer's disease (AD) pathology, with seizures occurring both in patients and in animal models of the disease. We know from studies of epilepsy that dysfunction in the inhibitory system often underlies this type of activity and this marries well with the increasing body of evidence showing the alteration and loss of interneurons during the course of the disease. Interneurons are highly heterogeneous and understanding the way in which the interneurons networks are affected may provide clues to factors that make neurons particularly susceptible to the disease pathology.

Focusing on the CA1 region of the hippocampus, the first hippocampal sub-region to be affected by AD pathology and the focal point of many forms of epilepsy, the presented work investigates changes in GABAergic synaptic density in J20 APP(Swe/Ind) transgenic at ages preceding overt plaque pathology. To quantify GABAergic synaptic density, we used the colocalisation of immunofluorescence staining against GABAergic synaptic marker (VGAT and gephryin), and compared the layer specific (stratum oriens, stratum pyramidales, stratum radiatum, statum lacunosum moleculare) synaptic density along the dorsal-ventral axis. For each layer a gradient was generated using linear regression (WT n=4, J20 n=4; str. or: WT= 8.7 x10-4±2.1x10-4, J20=-6.8x10-4±4.2x10-4; str. pyr: WT=-1.7x10-4±3.4x10-4, J20=-4.5x10-4±4.5x10-4; str. rad: WT=8.2x10-4±3.2x10-4, J20=-8.4x10-4±9.0x10-4; str. LM: WT=7.4x10-4±3.6x10-4, J20=-9.3x10-4±7.1x10-4).

As different functional subpopulations of interneurons synapses in specific sub-layers of the hippocampus the findings of the study will inform future investigations into identifying the structural and functional changes to the CA1 inhibitory circuitry in AD pathology. Understanding these changes may elucidate the mechanisms that underlie altered network function during disease progression and allow for the development for selective therapeutics targeting the GABAergic system.

Poster Ref: P2-F-035

Theme: F: Nervous System Disorders

Behavioural characterization of sub-acute and acute MPTP mouse models of Parkinson's disease.

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Background: Parkinson's disease (PD) is the second most common neurodegenerative disorder, characterised by the selective loss of dopaminergic neurones in the nigro-striatal pathway. The disease is characterised by motor and non-motor related symptoms. PD is diagnosed based on motor-related symptoms, but more than 60% of patients also present with non-motor and cognitive symptoms and these appear years or sometimes decades before the disease is diagnosed.

Objective: We here present a complete behavioural characterisation of two MPTP models of PD in mice to identify behavioural endpoints that are relevant as translational biomarkers and can discriminate at a sufficiently robust level so much so that treatment-induced recovery of function in future pharmacological trials is potentially possible.

Methods: Male mice C57BL/6J eight weeks old were injected with a sub-acute (30 mg/kg once a day for 5 consecutive days) and acute (four injections of 20 mg/kg each 2 hours) regimen of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). For each model control mice were injected with saline. A battery of behavioural tests was performed in each model to investigate motor coordination, depression-anxiety traits and cognitive dysfunction. Behavioural readouts are correlated with histochemical assays of dopaminergic neurons in the substantia nigra and dopaminergic fibres in the striatum.

Results: Behavioural differences have been identified between controls and MPTP treated animals accounting for motor and non-motor symptomatology. Transitory differences have been observed for locomotor activity. Cognitive impairment has been observed in one of the MPTP models.

Conclusions: Drug trials of neuroprotective compounds are now possible for the different mouse models of MPTP. Behavioural biomarkers identified in this study will be used to evaluate their efficacy on symptomatology correlated with histological and biochemical assays to estimate neuroprotection and recovery.

Poster Ref: P2-F-036

Theme: F: Nervous System Disorders

Intrinsic properties of hippocampal CA1 stratum oriens neuronal subpopulations in different Aβ-overexpressing transgenic mouse models of amyloidopathy.

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Memory encoding in the hippocampus relies on a precise functional balance between excitation and inhibition, an equilibrium that is compromised in Alzheimer's disease (AD). Classification of GABAergic interneuron subtypes is based on their morphological, electrophysiological and molecular properties. However, this classification system may be compromised when dealing with a neuropathology, as these criteria may introduce an allocation bias. Here we introduce a new approach based on hierarchical cluster analysis of neuronal intrinsic excitability (IE) properties in order to identify neuronal subpopulations located in hippocampal stratum oriens (SO) in amyloid β (Aβ)-overexpressing transgenic mice and wild-type (WT) controls. Using this approach, we assessed the effect of AD-like genotypes on IE in these subpopulations.

Horizontal hippocampal slices were prepared from PDAPP and TAS-TPM mice and their respective age-matched WT controls. Whole-cell current clamp recordings were made from neuronal somata located in SO. Cells were loaded with biocytin and, following fixation and staining, were subsequently traced. For subpopulation allocation, we considered the values of three IE properties: sag, input resistance (Ri) and afterhyperpolarization (AHP). Hierarchical cluster analysis was performed using a custom written Matlab routine.

Putative pyramidal oriens-subiculum neurons (POS), trilaminar (TL) and oriens-lacunosum moleculare (O-LM) interneurons were identified from each genotype and their IE properties were compared to their respective controls (see table for results). The comparison included subthreshold properties (*i.e.* resting membrane potential, Ri, sag, capacitance, resonance), firing dynamics, action potential waveform and post-burst events (*i.e.* AHP).

This study offers a tool for describing interneuron subpopulations in models of neuropathology. This is, to our knowledge, the first systematic description of AD-related IE alterations in hippocampal interneurons. We observed various effects of amyloidopathy on each neuronal subpopulation, with a trend towards hyperexcitability. This finding is in accordance with our previous observations on CA1 pyramidal neuron IE properties, whilst also highlighting the complexity of alterations in different cell subtypes.

Putative neuronal subtype	Differences in IE properties (p<0.05)	
	PDAPP	TAS-TPM
POS	↓ AP width ↓ AP Peak ↑ AP RoR ↑ Firing rate ↑ Peak Z	↓ AP width ↑ AP AHP ↓ Firing rate
TL	↓ AP width ↑ AP RoR ↑ AP AHP ↓ Peak Z	↑ Ri ↑ Firing rate ↓ Post-train AHP ↑ Peak Z
O-LM	↓ RMP ↓ AP RoR ↓ AP AHP	↑ Firing rate ↓ Q

Differences in IE properties amongst SO neuronal subtypes in two different Aβ-overexpressing transgenic mouse lines. Arrows indicate a significant difference ($p<0.05$) between each transgenic genotype and respective WT control. AHP, afterhyperpolarization; AP, action potential; Q, quality factor of the resonator; RMP, resting membrane potential; RoR, max rate of rise; Z, impedance of the resonator.

Poster Ref: P2-F-037

Theme: F: Nervous System Disorders

An evaluation of unfolded protein response pathways in relation to amyloid and tau pathology in human Alzheimer's diseases.

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Recent evidence has implicated endoplasmic reticulum stress or "unfolded protein response" (UPR) in several proteinopathy-based neurodegenerative diseases including Alzheimer's disease (AD). Despite the potential of the UPR to be exploited for AD treatment, a systematic assessment of key UPR markers within categorised human AD cases is still elusive. This information is essential to determine the time course of UPR activation and its relevance in disease onset and progression.

Post-mortem temporal cortex samples (Brodmann area 21) from non-AD and AD diagnosed individuals were assessed for traditional markers of AD (amyloid: 6E10 and MOAB-2, Tau: HT-7, and phospho-tau; PHF1) alongside key regulators of UPR, double stranded-RNA-dependent protein kinase-like ER kinase (PERK), inositol-requiring enzyme 1 (IRE1), activating transcription factor-6 (ATF-6), eukaryotic initiating factor 2α (eIF2α) and the apoptotic transcription factor CHOP using Western and dot blot techniques.

Immuno-blots for oligomeric amyloid (soluble lysates, MOAB-2 dot blot), aggregated tau (insoluble HT-7 western blot) and phospho-tau (soluble and insoluble PHF-1 western blots) were robustly elevated in AD samples compared to non-AD samples (all p's<0.05). Corresponding measurements within the same samples demonstrated a trend for the elevation of the UPR initiator IRE1α in AD cases ($p=0.07$). Further correlation analysis (immuno-blot signal vs Braak staging) reported significant correlations for oligomeric amyloid, aggregated Tau and soluble phospho-tau as well as for total IRE1 ($r>0.7$ for all), but not for monomeric amyloid. Together, these data suggest a graded expression of IRE1 may be driven by UPR activation during degenerative processes.

Additional UPR markers including UPR initiators PERK and ATF-6 as well as downstream targets of the stress response eiF2α and CHOP are currently being quantified and investigated for correlations with amyloid and tau pathology as well as with Braak staging.

Establishing the relevance of UPR to early dementia stages in human cases of AD, and the relationship between UPR mediators and traditional amyloid and tau pathology, will allow an evaluation of its causative role in the pathogenesis of dementia.

Poster Ref: P2-F-038

Theme: F: Nervous System Disorders

Long-term seizure profile, clustering and intra-cluster seizure dynamics in the tetanus toxin model of temporal lobe epilepsy.

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Epileptic seizures are traditionally considered to be sudden and random events. The seemingly random occurrence of seizures represents one of the main disabling features of epilepsy. Recently, several studies have identified the existence of periods of increased and decreased probability of seizure occurrence in chronic models of epilepsy. In the current study, we examined the long-term seizure dynamics in the tetanus toxin model of temporal lobe epilepsy using approaches from the field of complex system dynamics.

Tetanus toxin was stereotaxically injected into the right hippocampal CA3 area of seven adult rats, and silver ball electrodes were implanted epidurally above the hippocampi. Continuous video-EEG monitoring was initiated on day four and continued for two weeks, to monitor the development of spontaneous seizures.

All animals developed spontaneous seizures characterized as complex partial seizures, which could be followed by secondarily generalization. Animals experienced 109±22 (median 103) seizures during the recording period. The seizure duration was 118±13 (median 112) seconds and the interval between seizures was 118±28 (median 91). Statistical analysis of seizure profiles revealed that distribution intervals between seizures differs from a random Poisson process, due to accumulation of seizures into clusters. Analysis of intra-cluster seizure profiles and comparison with surrogate data revealed the presence of internal dynamics of seizure distribution characterized by a progressive increase in the duration of inter-seizure intervals towards the cluster termination.

This study reveals that seizures in the tetanus toxin model of temporal lobe epilepsy are not randomly distributed due to the presence of seizure clusters and intra-cluster seizure dynamics. The time of seizure occurrence may be predictable on a longer time scale and understanding of the long-term fluctuations in seizure probability is a crucial prerequisite for elucidating mechanisms of ictogenesis and for the development of more reliable techniques of seizure forecasting.

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Poster Ref: P2-F-039

Theme: F: Nervous System Disorders

Function and regeneration of dopaminergic neurons in the brain of zebrafish.

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The dopaminergic system of the zebrafish is believed to be evolutionarily conserved with comparable dopaminergic populations found in the brain of mammals. Dissimilar however to mammals the zebrafish is known to be capable of regenerating various types of neurons and their axons. Thus the zebrafish dopaminergic system provides an excellent model to study replacement of a specific and important cell type in the adult CNS. We have developed a novel toxin ablation paradigm through which we can specifically ablate select groups group of dopaminergic (DA) cells in the adult zebrafish diencephalon, leaving other dopamine populations unaffected. One of these group of diencephalic cells are the only source of dopaminergic spinal innervation. This is supported by a loss of DA spinal axons following our toxin ablation. The diencephalic population ablated by the toxin has been suggested as the most likely candidate for a zebrafish homologue of the mammalian nigro-striatal pathway. The loss of cells is very specific and reproducible, indicating that these cells are particularly vulnerable to the toxin. We have carried out histology at various time-points post ablation to determine the capacity for regeneration of DA neurons in the CNS of zebrafish. This revealed that some populations returned to control numbers whereas others only partially recovered even after 6 months. We have shown that this recovery is due to neurogenesis; furthermore, by inducing inflammation after the toxin treatment we can accelerate the recovery of dopaminergic cell numbers by 50%.

As the toxin treatment results in such a targeted cell loss we aimed to investigate the function of this group of ablated neurons through a battery of behavioural tests. These tests revealed deficits in the toxin treated animals' ability to perform in fine movement tests such as maintaining shoal cohesion and breeding behaviours, whereas general movement was not impaired. We now aim to further investigate by what means the dopaminergic neurons are regenerated and which progenitors are responsible. Ultimately, understanding how zebrafish functionally regenerate dopaminergic neurons may inform research into neurodegenerative diseases, such as Parkinson's Disease.

Funding: MRC and BBSRC

Poster Ref: P2-F-040

Theme: F: Nervous System Disorders

Metabotropic glutamate receptor function in *C. elegans* behaviour.

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Glutamate signalling in the mammalian central nervous system performs an important role in excitatory transmission. Glutamatergic neurotransmission occurs through two classes of receptor, ionotropic receptors (iGluRs) and metabotropic receptors (mGluRs). The mGluRs perform an important neuromodulatory role in the mammalian central nervous system, where 8 different mGluR subtypes have been identified and divided into 3 distinct subgroups. Group I mGluRs are of particular interest, as they have been implicated in Fragile X Syndrome, a genetic condition that falls within the autism spectrum of disorders, pain processing and movement disorders.

The *C. elegans* genome contains 3 mGluR subtypes, mgl-1, mgl-2 and mgl-3. Behavioural and electrophysiological analysis has identified mgl-1 as an important modulator of neuronal circuits that control the feeding behaviour of *C. elegans*. Here, we extend our analysis of this class of receptor to investigate mgl-2, the *C. elegans* orthologue of the mammalian Group I mGluR. The analysis of a transgenic line expressing the MGL-2 receptor fused to GFP at the C-terminal (MGL-2::GFP) suggests that MGL-2 is expressed within the nervous system of *C. elegans*. In previous studies mgl-2 has been described as being expressed within interneurons that perform an important role in the modulation and integration of signalling within sensory pathways. Hence, to further assess the function of mgl-2 in *C. elegans* we have conducted a combination of behavioural assays that require the worm to integrate sensory information. In doing so we have identified that worms expressing a functional knockout of the receptor encoded by mgl-2 are impaired in their ability to integrate sensory information. To validate the phenotypes observed are driven by MGL-2, the MGL-2::GFP fusion has been expressed in the mgl-2 mutant background and rescues the behavioural phenotypes. Understanding how metabotropic glutamate signalling is organised could provide further insight into neurological conditions, where glutamatergic neurotransmission is disrupted culminating in impaired neuromodulation and signal integration.

Poster Ref: P2-F-041

Theme: F: Nervous System Disorders

Phytochemical, anti-acetylcholinesterase, -oxidant, and -inflammatory profiles of selected Jordanian medicinal plants: potential for neurodegenerative disease.

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The study aimed at evaluating the therapeutic potentials of six traditional medicinal plants used in Jordan for the improvement of memory in old age. The anti-inflammatory, anti-cholinesterase and anti-oxidant properties of the medicinal plant methanol extracts were investigated. Phytochemical analysis for the total phenolic and flavonoid contents of these plants was also carried out using spectrophotometric methods. AChEI, anti-oxidant, COX inhibitory and metal chelating activities were determined. *A. citrodora* and *P. harmala* root and seeds showed modest inhibitory effects on AChE (mean IC50 68,100 and 93 µg/ml, respectively). *A. microcarpus*, *I. viscosa* and *A. citrodora* displayed COX-1 enzyme inhibitory activity (mean IC50 34.9, 3.4 and 3.2 µg/ml, respectively). Potent DPPH radical scavenging activity was demonstrated by all tested plants. Two extracts (*A. andrachne* and *A. microcarpus*) exhibited potent NO scavenging activity (mean IC50 4.5 and 5.0 ug/ml, respectively). Three extracts *A. citriodora*, *P. harmala* (Root) & (seed) and *A. microcarpus* exhibited potent metal chelating ability (mean IC50 4.5, 6.2, 6.5 and 6.7 µg/ml, respectively). The reversible interaction against AChE, moderate activity against COX-1, potent antioxidant activity and strong metal chelating ability make these plants promising new products for further investigation *in vivo*, either as total extracts or as single bioactive constituents. *A. andrachne* and *A. microcarpus* extracts should be further evaluated since they exhibited promising nitric oxide (NO) scavenging activities. The results obtained in this study suggest the potential use of plants in Jordanian traditional medicine for age-related neurological diseases.

Poster Ref: P2-F-042

Theme: F: Nervous System Disorders

Neuroprotective effect of 3α5β-pregnanolone glutamate in the early stage of the immature rat ischemia. Histological and neurochemical properties.

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Hypoxic-ischemic damage is the most common form of perinatal brain damage that threatens newborns life and leads to permanent neurological consequences. A key role in the development of a permanent structural and functional disability play a complex molecular processes running to ischemic cascade connecting with glutamate. Although the importance of the glutamatergic toxicity in ischemia is studied, its mechanisms are not fully understood and a little attention has been paid to this process in the perinatal age.

The neuroprotective effects of steroid antagonists of NMDA receptors having the potential to be used as a better-targeted and more effective treatment of postischemic damage was demonstrated. The neuroactive steroid 3α5β-pregnanolone glutamate (PG), synthetic analog of naturally-occuring 3α5β-pregnanolone sulphate, is a NMDA receptor negative modulator and GABAA receptor positive modulator acting *via* use-dependent mechanism.

Purpose: to elucidate effect of PG treatment in the model of focal cerebral ischemia in immature rats.

Focal ischemia was induced by infusion of endothelin-1 (ET-1; 40pmol/1µl) into the right dorsal hippocampus (1.5% isoflurane) in 12 days old Wistar rats. PG was intraperitoneally applied 5min after the ischemic insult (doses 1 or 10 mg/kg). We focused on using immunohistochemistry methods (24h and later intervals) and monitoring of neurochemical changes using microdyalisis.

ET-1 infusion led to massive hippocampal neurodegeneration while PG treatment significantly reduced neurodegeneration of pyramidal and granule cells in the afflicted hippocampus (FJB staining). Intraperitoneal administration of this agent also protected of PVA-positive interneurons, reduced activation of microglia and astrogliosis. The results from microdialysis measurement demonstrated reduced lactate acidosis and production of reactive nitrogen species after PG treatment.

Our results suggest neuroprotective effect of the PG treatment in the used model. This agent has a positive effect on all examined parameters of stroke. PG represents a novel drug acting as GABAA and NMDA receptor allosteric modulator to treat perinatal ischemia.

This study was supported by GACR grants P304/12/G069, P304/14/20613S, TACR-TE01020028 and institutional support RVO: 67985823.

Poster Ref: P2-F-043

Theme: F: Nervous System Disorders

The LINC to SOD1 mediated amyotrophic lateral sclerosis (ALS).

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Mutations in superoxide dismutase 1 (SOD1) cause familial amyotrophic lateral sclerosis (ALS). Since this discovery in 1993 a number of disparate defective genes have been identified, suggesting that multifactorial mechanisms underpin ALS pathology, yet the exact molecular mechanism remains to be elucidated. The evolutionary conserved LINC complex (Linker of the Nucleoskeleton and Cytoskeleton) is composed of nesprins, SUN-domain proteins, emerin and lamins, which bridges the nuclear envelope (NE), hardwiring the genome to cytoplasmic organelles and the cytoskeleton and thus plays an important role in cell architecture and signalling. Mutant G93A-SOD1 aggregates at various cellular membranes including the ER, which is continuous with the NE. Therefore, we suggest that potential LINC complex disruption by mutant G93A-SOD1 may cause cellular structural instability, contributing to motor neuron demise. The aim was to explore our hypothesis in an *in vitro* model system by culturing NSC34 cells, which is a well-used motor neuron model, and CAD (Cath.a differentiated) cells, a dopaminergic cell line, as subclinical dopaminergic dysfunction is present in a subset of fALS cases and an ALS transgenic mouse model has shown midbrain dopaminergic degeneration. These cell lines can be differentiated in culture spontaneously or by simple serum removal, respectively. These cells were transiently transfect them with Wt-hSOD1 and G93A-SOD1 and any possible LINC complex disruption analysed *via* immunofluorescence and western blot techniques. Our results show that key LINC complex proteins undergo changes in intracellular location as NSC34 cells differentiate, with increased expression at the nuclear envelope being the most common finding. Notably, the intracellular location of emerin in undifferentiated NSC34s and CADs is cytoplasmic and granular in appearance while in differentiated cells it is more concentrated at the NE. Moreover, both Wt-hSOD1 and G93A-SOD1 overexpression yields a pronounced emerin protein aggregation in the cytoplasm. These results suggest that key LINC complex proteins are dynamic and adapt to the cells structural requirements in NSC34s. In addition, emerin perturbation, seen in both Wt-hSOD1 and G93A-SOD1 transiently transfected cells, leads to possible disruption of the LINC transcellular complex.

Poster Ref: P2-F-044

Theme: F: Nervous System Disorders

The effect of ischaemia on the DUSP-4 knockout mouse.

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MAPK's (mitogen-activated protein kinases) play an important role in transducing stress-related signals by a cascade of intracellular kinase phosphorylation and transcription factor activation that regulate inflammatory gene production. The three main MAPK signalling pathways, ERK1/2, JNK and p38, have been reported to play crucial roles in neuroinflammation and neurogenesis. MAPK phosphatases (MKPs) act as negatively regulators of the MAPK pathway and thereby have potent immunomodulatory actions which could play a role in improving neurogenesis and stem cell function. The present work examined the effects of DUSP-4 (MKP-2) knockout (KO) on cerebral ischaemia with the ultimate aim of better understanding immune cell-stem cell interactions. This is the first time DUSP-4 KO mice have undergone *in vivo* surgery. All procedures were in accordance with the Home Office and local ethical guidelines and ARRIVE guidelines were adhered to. Male (25-30g) WT (n=4) and DUSP-4 KO mice on a C57 black background (n=5) underwent 45 min transient focal ischaemia with 72 hours reperfusion. Randomisation was achieved through coin toss and allocation concealment was achieved by independent investigator. One mouse (DUSP-4 KO) was excluded according to exclusion criteria of lack of blood flow deficit (as measured by laser Doppler) during occlusion period. Preliminary results show that DUSP-4 KO mice had increased mortality and morbidity due to increased haemorrhaging at the wound site (n=2) and possibly increased brain swelling (n=2) whereas all WT mice recovered well following surgery. Cerebral blood flow deficit and neurological deficit were not influenced in DUSP-4 KO however in knockout mice (n=2) hyperperfusion was evident post-reperfusion (n=2 [an increase up to 195% and 240%]). In conclusion, these results reveal potential complications of DUSP-4 KO mice undergo surgery and further work is required to establish whether this is related to effects of inflammation on coagulation.

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Poster Ref: P2-F-045

Theme: F: Nervous System Disorders

Decreased volume of subcortical structures in migraine patients with aura.

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Introduction: Migraines affect up to one in three people at some point in their lives and can be extremely debilitating, affecting the quality of life of sufferers. In some cases patients experience a premonitory phase prior to an attack, known as migraine with aura (MA), the symptoms of which can mimic other conditions including minor stroke. However as yet there is only a limited understanding of the pathophysiology of migraine, with neuroimaging providing a promising means of seeking potential biomarkers and therapeutic targets. In this study we compare the volume of subcortical structures in MA patients relative to healthy controls.

Methods: High-resolution T1-weighted scans were obtained as part of a diagnostic protocol from 14 patients diagnosed with MA (mean age: 41±11, 21-55) at baseline and 14 healthy controls with no history of migraine (mean age: 31±7, 21-45). Automatic subcortical segmentation was performed using Freesurfer. SPSS 22 was used to perform an ANCOVA for each subcortical region with age and total intracranial volume included as covariates.

Results: Significant differences ($p<0.05$) were found between the control and patient groups. Specifically the volumes of the left thalamus ($F=6.157$, $p=0.021$), left amygdala ($F=8.102$, $p=0.009$), left ventral diencephalon (DC) ($F=5.910$, $p=0.024$), right thalamus ($F=11.456$, $p=0.003$), right pallidum ($F=11.371$, $p=0.003$) and right ventral DC ($F=5.807$, $p=0.025$) were significantly lower in the MA group relative to the healthy controls.

Conclusion: The results accord well with previous research where differences in the microstructure of the thalamus for MA relative to migraine without aura patients and healthy controls have been reported. Decreased volume in subcortical structures for migraine without aura patients have also been noted. The thalamus, which has a key role in regulating motor function and sensory perception, is thought to act as a hub in integrating and transmitting pain in migraine. Meanwhile functional studies have reported differences in response within the pallidum and amygdala. Further work is required to investigate the nature of these changes more fully, in particular whether the differences are present in such patients generally or as a consequence of experiencing MA over a prolonged period.

Poster Ref: P2-F-046

Theme: F: Nervous System Disorders

The contribution of inhibitory interneuron pathology to neurological deficits in mitochondrial disease.

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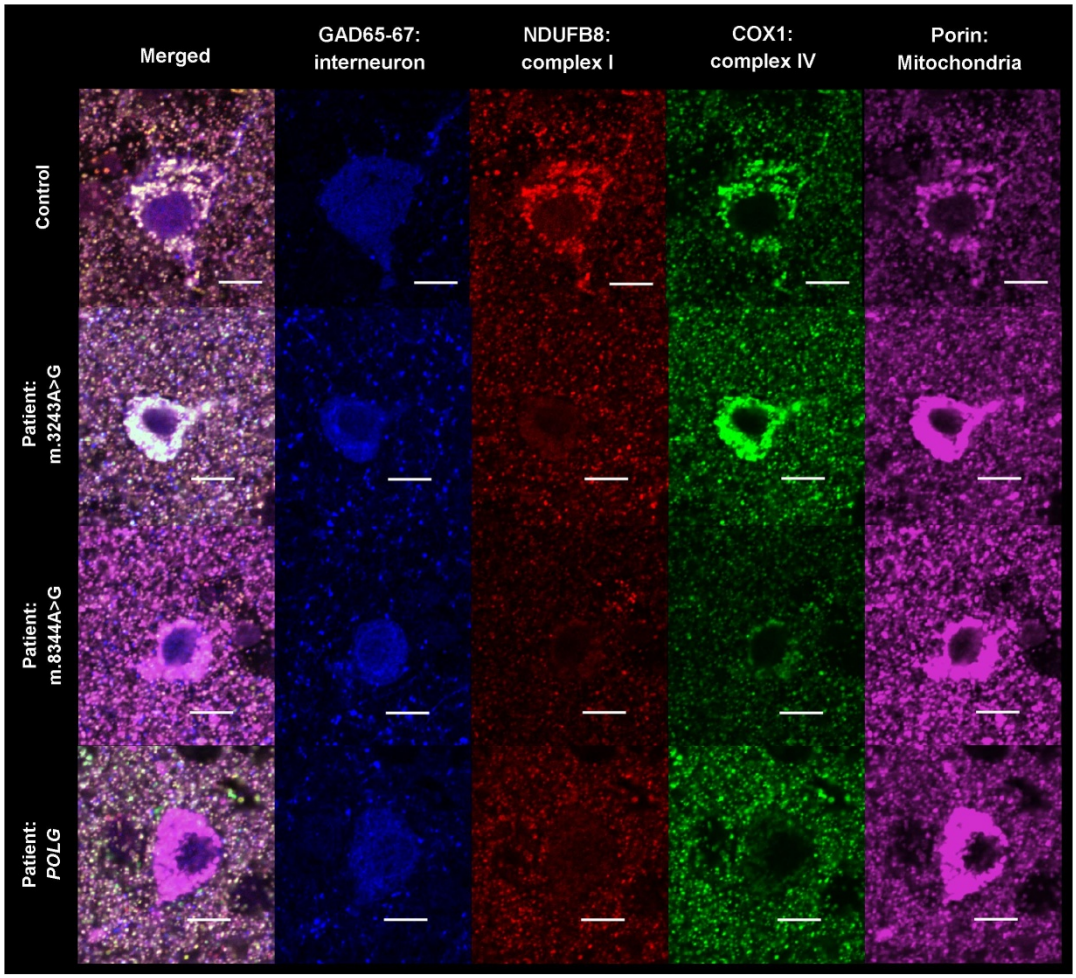
Patients that harbour mitochondrial DNA mutations or mutations in nuclear genes involved in mitochondrial maintenance will develop mitochondrial disease. Symptoms associated with mitochondrial disease are heterogeneous though neurological deficits are common and most debilitating. We still do not understand the specific involvement of certain brain regions in mitochondrial disease or indeed selective neuronal vulnerability.

Here we performed an extensive neuropathological investigation of ten patients with clinically and genetically confirmed mitochondrial disease and ten age-matched control individuals. Since previous studies suggest a vulnerability of interneurons to mitochondrial respiratory chain impairment, particularly complex I, we applied a quantitative immunofluorescent method to interrogate complex I and IV protein expression in the mitochondria of GABAergic interneurons in frontal, temporal and occipital cortices. We evaluate the density of inhibitory interneuron to pyramidal neurons to determine whether there is a preferential loss of a particular subclass of neuron.

We observe a significant and global reduction in complex I expression within GABAergic interneuron populations in frontal, temporal and occipital cortices in all patients (Figure 1). While complex IV expression is variable there is reduced expression in those patients harbouring m.8344A>G point mutations or POLG mutations. In addition to severe respiratory chain deficiencies within remaining populations of inhibitory interneurons, quantification of GABAergic cell density shows a dramatic reduction in all patients indicative of cell loss. This was confirmed when pyramidal neurons were investigated where ratios of GABAergic to pyramidal neurons were markedly reduced in patients relative to controls.

This suggests that the balance of excitation to inhibition may have shifted in mitochondrial disease and might contribute to impaired neuronal network oscillations. This study provides evidence that inhibitory interneurons are particularly vulnerable to mitochondrial DNA defects and implicate interneuron dysfunction which might underlie the pathogenesis of several neurological disorders, including cognitive impairment and epilepsy in patients with mitochondrial disease.



Immunofluorescence allows visualisation of mitochondrial respiratory chain proteins including complexes I and IV in conjunction with mitochondrial mass within interneurons in temporal cortex. Control interneurons show equal expression of complexes I and IV and mitochondria. In m.3243A>G, there is a specific loss of complex I while m.8344A>G and POLG show a combined loss of complexes I and IV.

Poster Ref: P2-F-047

Theme: F: Nervous System Disorders

The effect of food restriction, voluntary exercise, and of their combination (activity-based anorexia –ABA) on GABA-ergic inputs onto somata of the dorsal hippocampal CA1 Pyramidal cells of adolescent female rats.

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Anorexia nervosa (AN) is a severe eating disorder with the highest mortality rate among psychiatric conditions. It affects mostly women, with the onset typically during adolescence. Once an individual develops AN, it is likely that the suffering continues throughout her life due to its high relapse rate. There are no FDA-approved drugs for AN so far. Hence, it is urgent that we examine the neurobiology underlying AN for developing better treatments. This study employs the animal model of anorexia, called activity-based anorexia (ABA), to examine the neurobiological changes associated with fasting and hyperactivity, two characteristic symptoms of AN. 32 female adolescent rats (P36) were divided into four groups of 8 animals: control (CON), ABA, food restriction only (FR), and exercise only (EX). ABA and EX groups underwent 8 d of voluntary exercise, from P36 to P44. ABA and FR groups underwent 4 days of food restriction (1 h per day access to food), from P40 to P44. By P44, ABA and FR rats lost 20% of their body weight compared to baseline. After food restriction, ABA rats increased wheel activity significantly more than EX rats. The ABA group exhibited a wider range of activity levels than the EX group, suggesting an exaggeration of individual variability in activity level when coupled with food restriction. This may underlie the division between the vulnerable and the resilient to the ABA condition. The CA1 region of dorsal hippocampus is important for spatial cognition and anxiety regulation. At the end of the behavioural phase of the experiment (P44), animals were euthanized for quantification of the number of GABA-ergic axon terminals contacting pyramidal neuron somata in this region by electron microscopic immunocytochemistry. This number was significantly reduced for FR tissue, compared to CON. However, no difference was detected for ABA tissue, compared to CON. This may indicate that the exercise that ABA rats underwent attenuated the fasting effect. The GAD-labeled terminal length was negatively correlated with the activity level on the last day, but only for the ABA rats. Our results show that the combination of fasting and exercise, or the ABA model, produces different behavioural and neurobiological effects from either fasting or exercise alone.

Poster Ref: P2-F-048

Theme: F: Nervous System Disorders

Inflammation-Induced changes in depressive-like behaviour in the mouse female urine sniffing test.

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The female urine sniffing test (FUST) is a novel paradigm that exploits the ability of female urine to elicit behaviour associated with sexual motivation in male mice (Malkesman *et al.*, 2010). The FUST can be used to assess depressive-like behaviour thought to reflect the loss of sex drive seen in depressed patients (Baldwin, 2001). We investigated whether the FUST is able to detect changes in the acute lipopolysaccharide (LPS) model of inflammation-induced depression and assessed the antidepressant potential of ketamine.

Adult male C57BL/6J mice (10-14 weeks, n=6-11) were exposed to two cotton applicators soaked in water or urine for a 3-minute test period. Time spent sniffing either applicator was calculated. Mice were injected with 0.83mg/kg LPS or saline (10ml/kg, i.p.) 24 or 6 hours prior to FUST. 10mg/kg ketamine (10ml/kg, s.c.) was administered either 24 hours or 30 minutes prior to FUST. Data were analysed by 2-way ANOVA followed by Bonferroni posthoc.

Mice spent significantly more time sniffing female urine over water and male urine, with increases of 240% and 120%, respectively ($P<0.001$). Mice did not spent significantly more time sniffing male urine over water. Subsequently, acute LPS caused a significant reduction in time spent sniffing female urine at both 6 and 24 hours after injection, with reductions of 80% and 60% respectively ($P<0.001$). Ketamine failed to attenuate the depressive effects of LPS when administered either 24 hours or 30 minutes prior to testing. In the absence of LPS, ketamine administered 30 minutes before FUST reduced time spent sniffing urine by 40% ($P<0.01$).

The sniffing preference seen with female urine is likely to be motivated by sex, not novelty, as the same behaviour is not seen with male urine. The LPS-induced reduction in sexual motivation suggests that FUST is sensitive to detecting inflammation-induced depressive-like behaviours. Surprisingly, ketamine alone had a pro-depressive effect in the FUST and failed to abrogate the effects of acute LPS. However, previous studies have reported predictive validity in the FUST following chronic citalopram administration, suggesting the FUST may be more sensitive to chronic treatments.

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Poster Ref: P2-F-049

Theme: F: Nervous System Disorders

Identification of novel small molecule compounds that disrupt an auto-inhibitory intramolecular interaction in the Parkinson's disease associated E3 ligase, Parkin.

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Parkinson's disease (PD) is a progressive neurodegenerative disorder that remains incurable. Loss-of-function mutations in the Parkin gene are the commonest cause of familial early-onset Parkinson's disease. Parkin encodes a Ring–in-between-Ring E3 ubiquitin ligase that is reported to target multiple substrates implicated in diverse cellular processes including mitophagy, cell survival and vesicle trafficking, which may contribute to its known neuroprotective role. Biochemical and structural analysis of Parkin reveals it to exist in an autoinhibited conformation mediated in part by its N-terminal Ubiquitin-like (Ubl) domain (Chaugule *et al.*, 2011; Trempe *et al.*, 2014). Upon mitochondrial damage, Parkin is activated by phosphorylation at serine 65 within the Ubl domain by the mitochondrial serine/threonine kinase PINK1, which acts to disrupt an intra-molecular protein-protein interaction between the Ubl and RING1 domains. Dysfunction and failure to activate Parkin either by mutations in Parkin or the PINK1 gene in patients with familial PD, indicates that a drug which directly activates parkin could hold promise as a disease-modifying therapy for PD patients. Here we report the development of a high throughput AlphaScreen assay to measure the interaction between the Ubl domain of Parkin (GST-tagged) and a Ubl-deleted fragment of Parkin (biotinylated). The assay was employed to screen approximately 25,000 compounds from the Drug Discovery Unit (DDU) small molecule collection for ability to disrupt the Ubl-RING1 interaction. 256 active compounds were progressed for potency determination and ten hit compounds displaying pIC50 values greater than 4 identified. These compounds were re-purchased along with 45 commercially available analogues. In addition, 44 further analogues were selected from the remainder of the DDU compound library. Following an assessment of the potency of all 99 selected compounds, a total of 12 compounds were confirmed as hits capable of disrupting the Ubl-RING1 interaction in the AlphaScreen assay. In future work, these compounds will be assessed for their ability to activate Parkin *in vivo*.

Reference

Chaugule VK, Burchell L, Barber KR *et al.* (2011). EMBO, 30: 2853-67

Trempe J-F, Sauve V, Grenier K *et al.* (2013). Science, 340, 1451-1455

Poster Ref: P2-F-050

Theme: F: Nervous System Disorders

Investigating the mode of action of bipolar disorder treatment, valproic acid, in inositol-dependent signalling using a non-animal model.

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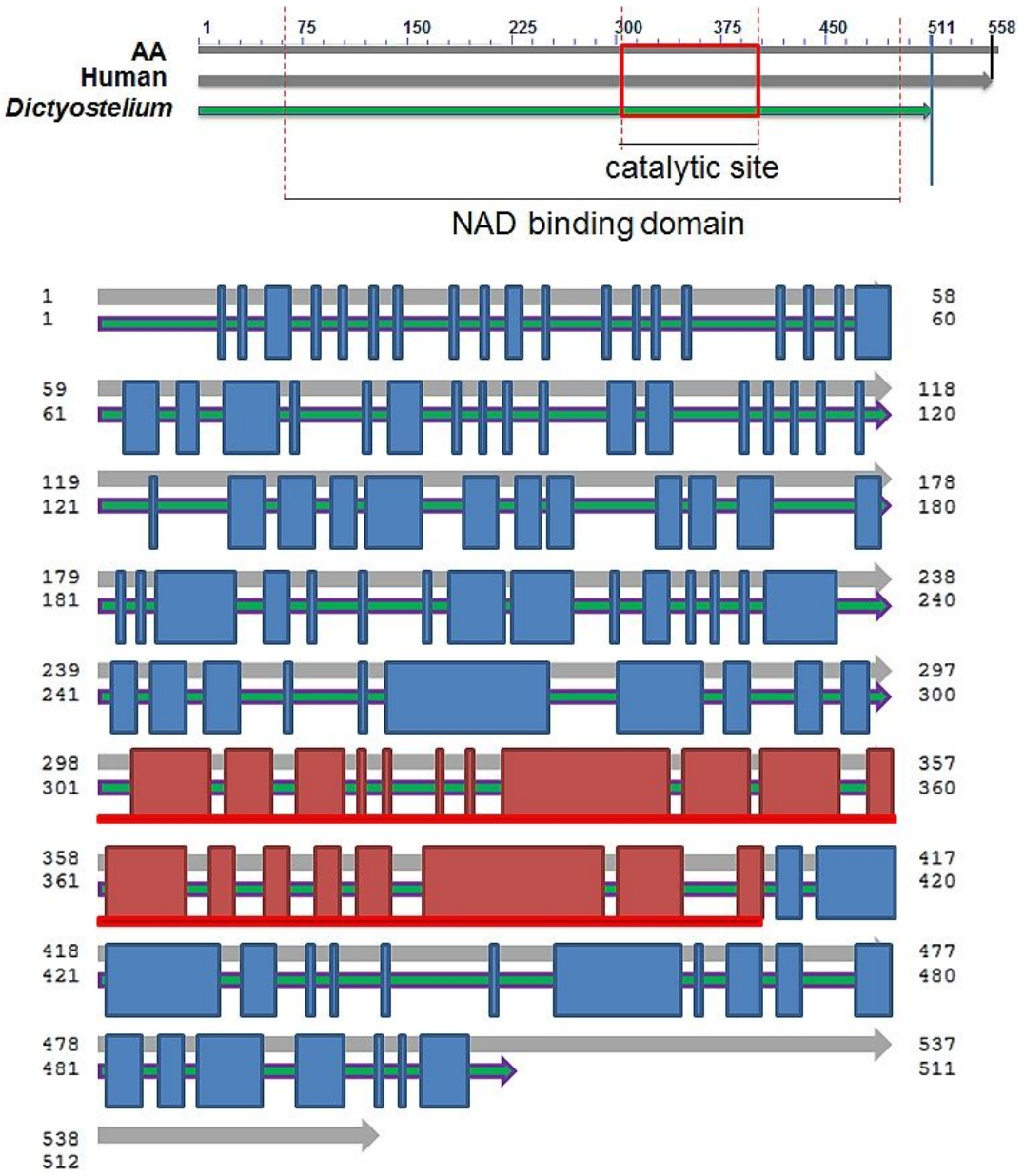
Regulating inositol signalling is a proposed mechanism of action for bipolar disorder treatments, including valproic acid (VPA) and lithium. Using a simple non-animal model, *Dictyostelium discoideum*, bipolar disorder treatments have been shown to reduce inositol (1,4,5)-trisphosphate (IP3) levels, leading to a block in development and a similar effect was then shown for three structurally distinct bipolar disorder treatments (including VPA) in a mammalian model. Although the mechanism by which VPA modulates inositol-dependent signalling remains unknown, it has been suggested to indirectly inhibit inositol-3-phosphate synthase (INO1) in *de novo* inositol biosynthesis.

In this study, we investigate a role for INO1 as a potential target for VPA and in basic cell function. We show that a cell line with ablated ino1 is unable to grow or develop unless supplemented with inositol. Cells die after inositol starvation for 24 hours, likely through an autophagy-dependent mechanism. Overexpression of ino1 rescues these effects, confirming a critical requirement for INO1 in growth and development. *Dictyostelium* cell lines with ablated or overexpressed ino1 remain sensitive to VPA during development, also suggesting that VPA does not act directly on INO1 during *Dictyostelium* development, but does not exclude indirect effects on INO1 activity. We then looked at the cellular and physiological effect of INO1 loss, by regulating the exogenous supply of inositol to the ino1- mutant. The absence of inositol caused a shift in *Dictyostelium* metabolism in a range of amino acids and hypoxanthine, lactate, putrecine, succinate and sn-glycero-3-phosphocholine and a reduction in specific phospholipid, indicating a key role for INO1 in cell function. We are also identifying potential INO1 binding partners that may provide both lead candidates for the direct effect of VPA on INO1 activity, and will help dissect the role of INO1 in basic cell function.

Our data provides a new insight into the cellular and physiological roles of INO1, including cell survival, metabolism and phospholipid signalling.

This project is funded by The Dr Hadwen Trust for Humane Research, the UK's leading medical research charity, funding exclusively non-animal research techniques to replace animal experiments.



Human (grey) and *Dictyostelium* (green) INO1 proteins are homologous. The proteins are of similar lengths, are 58% identical (blue boxes) including a highly conserved catalytic domain (red boxes). This suggests a conserved function for INO1 proteins and that *Dictyostelium* can be used as a model organism for the study of the effect of bipolar disorder treatments on inositol signalling.

Poster Ref: P2-F-051

Theme: F: Nervous System Disorders

Investigating the molecular mechanisms of hereditary spastic paraplegia neuropathies

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Hereditary spastic paraplegias (HSPs) are a large, genetically diverse group of disorders characterised by their progressive lower limb spasticity and pyramidal weakness. This defining clinical feature is thought to be caused by length-dependent axonopathy affecting the distal ends of the corticospinal tract axons, for which gene mutation is a major causative factor. However the genetic basis of many cases of HSP and the factors that control age-of-onset or severity remain unclear.

In many cases inherited mutations that lead to HSP occur in proteins involved in membrane trafficking and microtubule organisation. Identification of genetic mutations that contribute to inherited forms of HSP provides valuable insights into the molecular mechanisms and pathogenesis of this group of disorders, as well as providing some valuable insights into the cellular processes required for axonal maintenance or degeneration.

Our overall aim will be to improve our understanding of the pathogenic mechanisms that contribute to the onset and progression of HSPs. Although increasing numbers of genes are being identified, many HSP proteins remain poorly characterised with few known interaction partners and as such the molecular mechanisms of HSP progression remains poorly understood. We hypothesise those additional proteins, which interact with disease-causing HSP proteins may acquire novel disease-related mutations, contributing to HSP-related phenotypes. Therefore, identification of proteins that interact with known HSP proteins, or exist in common molecular complexes may provide insights into the molecular mechanisms of HSP pathology. We have begun by generating a high-density protein interaction network of human HSP-related proteins; this may provide insight into the molecular mechanisms of disease and identify new candidate genes for screening. Following this, we have used yeast two-hybrid techniques to test binary protein interactions identified, as well as identifying novel interaction partners for HSP proteins that have few or no known interaction partners.

The information generated will be crucial in our understanding of the cellular biology of HSPs, and could be applied to other neurodegenerative diseases involving axonopathy, such as multiple sclerosis.

Poster Ref: P2-F-052

Theme: F: Nervous System Disorders

Treatment with the omega-3 fatty acid docosahexaenoic acid reduces scar size and the upregulation of chondroitin sulphate proteoglycans following spinal cord injury.

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Queen Mary University of London

Spinal cord injury (SCI) results in devastating consequences due to the inability of the central nervous system to regenerate. This is partly due to the presence of a glial scar, rich in inhibitory chondroitin sulphate proteoglycans (CSPGs), which forms a physical and chemical barrier for regenerating axons. CSPGs are also highly expressed around certain neurons in perineuronal nets (PNNs). In the adult, PNNs limit CNS plasticity, but after SCI some functional recovery might be due to the re-emergence of plasticity within the damaged spinal cord. Treatments aimed at increasing plasticity may promote further recovery, but such treatments are sparse. Evidence from our laboratory shows that omega-3 polyunsaturated fatty acids, in particular docosahexaenoic acid (DHA), provide neuroprotection and improve functional recovery after SCI, and can promote neurite outgrowth *in vitro*.

We hypothesized that the beneficial effect of DHA after SCI may be due to a promotion of axonal growth and/or plasticity of intact systems, and/or a reduction in the expression of CSPGs, in addition to neuroprotection. Here, we examined the effects of treatment with DHA on neuronal plasticity following SCI, by focusing on changes in the expression of CSPGs in the extracellular matrix and in PNNs.

Hemisection injury was performed at thoracic level 12 in adult rats. Thirty min post-injury, rats received an acute intravenous injection of 500 nmol/kg DHA or of saline (controls) *via* the tail vein. After 2 or 8 weeks, animals were sacrificed, spinal cords removed, sectioned, and stained for PNNs, the CSPGs neurocan, versican, NG2, and link protein, in addition to GFAP, synaptophysin, and serotonin. Immunostaining was imaged and quantified for changes between groups.

DHA treatment reduced the lesion size, and resulted in decreased neurocan, NG2, versican, and GFAP immunoreactivity at the scar border, compared to controls. Neurocan immunoreactivity in PNNs, 1mm rostral and 3.5 and 4mm caudal to the lesion site, was reduced.

These results indicate that DHA improves functional recovery after spinal cord hemisection by reducing the levels of CSPGs at the scar border, which could facilitate axonal regeneration, and by decreasing neurocan expression within PNNs, which may promote synaptic plasticity.

Poster Ref: P2-F-053

Theme: F: Nervous System Disorders

Investigating the role of tau in Neurodegenerative disease through the development of human, clinically relevant disease models using hiPSC technology.

Stephanie Wallis

University of Bristol

In our efforts to treat those suffering from taupathies, revealing the biomolecular mechanisms dictating tau protein pathogenesis within the brain has become a priority. This project focuses on the development of clinically relevant, cell-based models of two taupathies: Alzheimer's disease (AD) and Frontotemporal Dementia with Parkinsonism linked to chromosome 17 (FTDP-17).

Control human induced pluripotent stem cells (hiPSC) were differentiated into basal forebrain cholinergic neurons (bfCNs) and cortical glutamatergic (CGNs). BfCNs are one of the prominent populations of neurons lost in AD, along with CGNs, which are also lost in FTDP-17. BfCNs were generated using a non-adherent, embryoid body culture system that exploits endogenous sonic hedgehog signalling. CGNs were derived through differentiation of a monolayer of hiPSC using dual SMAD inhibition.

The hallmarks of AD are accumulation of Amyloid-β (Aβ) protein plaques and tau tangles. To explore the pathways linking these two proteins and the molecular basis underlying the vulnerability of these neuronal populations, neurons were subjected to toxic insult through the application of Aβ oligomers. The discovery that mutations within MAPT, the gene encoding tau, are responsible for FTDP-17 established a direct relationship between tau and neurodegenerative disease. To research the culpability of the V337M MAPT mutation in tau pathogenesis, CGNs were differentiated from hiPSC reprogrammed from patients with this mutation. Using site specific phosphorylated tau antibodies, alongside antibodies against key tau kinases, the effects of Aβ oligomers and this mutation on tau pathogenesis has been investigated.

Ongoing work focusses on the relationships between hyperphosphorylated tau, tau kinases and possible pathways responsible for initiation of disease. Glycogen synthase kinase 3 (GSK3) is a tau kinase thought to be important in the hyperphosphorylation of tau. The use of a GSK3 inhibitor to evaluate the involvement of this kinase in tau pathogenesis is currently being employed.

This work has led to the development of tools to facilitate research into the underlying mechanisms of tau pathology in AD and FTDP-17, which will hopefully result in the identification of targets for drug development.

Poster Ref: P2-F-054

Theme: F: Nervous System Disorders

Acyl-ghrelin does not induce adult olfactory bulb neurogenesis but does protect new olfactory bulb neurones in a 6-OHDA model of Parkinson's disease.

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Ghrelin, an orexigenic gut hormone produced in response to calorie restriction, acts on the hypothalamus to stimulate the release of growth hormone (GH); promoting food intake and fat storage. However, accumulating evidence suggests that ghrelin may also have important extra-hypothalamic functions, such as enhancing synaptic plasticity and hippocampal neurogenesis. This study aimed to elucidate the role of ghrelin in modulating adult olfactory bulb neurogenesis (AOBN). First, we characterised the expression of the ghrelin receptor, growth hormone secretagogue receptor (Ghsr), using an immuno-histochemical approach in adult C57BL6 mice and GHSR-GFP reporter mice. The results show that Ghsr was not expressed in the sub-ventricular zone (SVZ) of the lateral ventricle, suggesting that acyl-ghrelin does not mediate a direct effect on neural stem cell (NSC) proliferation in the SVZ.

Second, we analysed cell proliferation in the SVZ of Ghsr-/- and wild-type littermate mice following a 7-day i.v infusion of saline or acyl-ghrelin. IHC analysis revealed no effect of genotype or treatment on the number of dividing Ki67+ cells in the SVZ.

Third, using a BrdU pulse-chase approach we determined the effect of exogenous acyl-ghrelin treatment on the generation of new adult born neurones in the rat olfactory bulb (OB). Consistent with our previous findings, there was no significant increase in the number of new adult born BrdU+ cells ($p=0.8482$) or Brdu+/NeuN+ neurones ($p=0.7388$) in the granule cell layer (GCL) of the OB.

Finally, to determine whether acyl-ghrelin exerts a protective effect on the formation of new neurones in the OB we used the rat medial forebrain bundle (MFB) 6-OHDA lesion model to attenuate AOBN. Our data confirmed that 6-OHDA lesion significantly attenuated AOBN. However, acyl-ghrelin pre-treatment prevented a lesion-induced decrease in new adult-born OB BrdU+/NeuN+ neurones compared to saline/lesion controls ($P<0.01$).

These data suggest that acyl-ghrelin does not affect AOBN directly. However, the hormone exerted a protective effect on AOBN in a rat model of Parkinson's disease, possibly by preventing dopaminergic denervation of the SVZ NSC's. Elevating acyl-ghrelin holds promise as a potential neuroprotective therapy for Parkinson's disease.

Poster Ref: P2-F-055

Theme: F: Nervous System Disorders

Fmr1 KO rats show deficits in hippocampus-dependent episodic memory but not in spatial reference and working memory.

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Much has been learned about the pathophysiology related to the loss of FMRP from mouse models of Fragile X syndrome (FXS), which is the leading identified cause of intellectual disability and Autism Spectrum Disorder (ASD). The recent generation of a rat model of FXS opens the door, not only to validate phenotypes across mammalian species, but also to address cognitive dysfunction using paradigms that are more difficult to address in mice. In this study we sought to test cognitive function in the Fmr1 KO rat, a rat model of FXS. Spatial memory of adult Fmr1 KO rats was assessed using two different protocols in the Watermaze: a reference memory and reversal task, and a delayed matching to place task. Fmr1 KO rats did not differ significantly from WT rats in acquisition or performance of either task, suggesting that spatial reference and working memory are intact. We also examined the development of episodic-like memory. Rats were tested in four spontaneous exploration tasks over two days: object recognition (OR), object-context (OC), object-place (OP) and object-place-context (OPC). This procedure was repeated 8 times between postnatal day 25 (P25) to adulthood (P71), to assess the development of the ability to discriminate novel from familiar objects, object-context, object-place and object-place-context associations. WT rats showed a significant preference for novelty, which developed earliest for OR, then OC, and finally OP and OPC. Fmr1 KO rats showed a similar developmental time course to WT rats in the OR, OC and OP tasks. In contrast, their ability to discriminate novel from familiar object-place-context (episodic-like) associations did not develop. A separate cohort of animals, tested only during adulthood, also showed preference for the novel stimulus in the NOR, OC and OP tasks, but not in the OPC task. The lack of spatial memory deficits in Watermaze tasks in Fmr1 KO rats together with a selective impairment in episodic-like memory in the object-place-context recognition task may suggest that shared pathophysiology between mice and rats manifests in unique behavioural deficits. These findings indicate that transgenic rats will complement existing mouse models, providing valuable insights into the effects of FMRP loss on cognitive function.

Poster Ref: P2-F-056

Theme: F: Nervous System Disorders

A protective role for ghrelin and GHSR on mid-brain dopaminergic neurones: therapeutic implications for Parkinson's disease.

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Parkinson's disease (PD) is a neurodegenerative disease affecting 1 in 100 people over the age of 60 and is characterised by motor and non-motor symptoms. PD symptoms usually appear upon the degradation of 60-80% of dopaminergic neurones in the Substantia Nigra pars compacta (SNpc). The aetiology of PD is unknown and current therapies lack long-term efficacy. Recent studies show that the orexigenic hormone, ghrelin, protects dopamine producing SNpc neurones in the murine MPTP model of PD. These findings have driven a new interest in elucidating ghrelin's neuroprotective mode of action.

Acyl-ghrelin mediates its action *via* the 7-transmembrane growth hormone secretagouge receptor (GHSR). GHSR is expressed extensively in the hypothalamus where its activation initiates GH release to increase appetite during calorie restriction. GHSR expression has been reported using immunohistochemistry (IHC) in many extra-hypothalamic sites, including the SNpc. However, antibodies raised against G-protein coupled receptors are often compromised due to a lack of specificity. Here we have characterised the expression of GHSR in the SNpc of adult GHSR-eGFP mice. Consistent with published findings, IHC against eGFP confirmed expression of GHSR in the SNpc. In this region, GHSR was co-expressed with TH and Girk2; therefore confirming ghrelin-receptor expression in the A9 dopaminergic neurone population that is preferentially lost in PD. Furthermore, we show that GHSR is expressed, using RT-PCR, western blotting and ICC, in the Girk2+ dopaminergic SN4741 cell line. We have used this neuronal cell line to develop a toxicity assay to investigate the potential direct effects of acyl-ghrelin.

First, we show that acyl-ghrelin (1uM) induces phosphorylation of the metabolic sensor AMPK ($P<0.01$), demonstrating that SN4741 cells are ghrelin-responsive. Second, we show that a 1-h pre-treatment with acyl-ghrelin (10nM & 100nM) directly prevents rotenone (10nM) induced dopamine cell loss in the same cell line ($P<0.05$). In addition, preliminary results show that under low glucose conditions acyl-ghrelin (100nM & 1uM) exerted a more pronounced protective effect on dopamine cells ($P<0.001$).

In summary, these data suggest that GHSR is a viable therapeutic target for PD.

Poster Ref: P2-F-057

Theme: F: Nervous System Disorders

Antioxidant, cytotoxicity and neuroprotective activity of endemic mascarene aloes.

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The present study aimed at evaluating the therapeutic properties of endemic Mascarene Aloes (*A. purpurea* Lam, *A. tormentorii*, *A. lomatophylloides* and *A. macra* Haw) and *Aloe vera*, extensively used in the traditional medicine. The antioxidant activity, cytotoxicity activity and neuroprotection properties relevant to neurodegenerative diseases were investigated. The free radical scavenging potential of the Aloes under study was evaluated using DPPH assay, and revealed that the 70 % (v/v) methanolic crude extracts of endemic Mascarene Aloes have potent radical scavenging properties. *A. purpurea* (Réunion Island) exhibited the highest radical scavenging potential, followed by *A. macrum* with an IC50 values of 0.334 mg/ml and 0.389 mg/ml respectively. *In vitro* cytotoxicity screening of crude methanolic extracts of the Aloes, using MTT cell proliferation assay indicated that the extracts of all the Aloes except *A. macra* elicited no toxic effect upon CAD neuronal cells at concentrations up to 0.1 mg/ml. The crude Aloes extracts (0.01 and 0.1 mg/ml) showed differential concentration-dependent neuroprotective characteristics against the toxic effects of hydrogen peroxide (250 µM) in CAD cell cultures, ranging from approximately 50 % to 100%. This study provides the first evidence for potent anti-oxidant and neuroprotective properties for a range of endemic Mascarene Aloe plant species, which requires further investigation *in vivo*.

Poster Ref: P2-F-058

Theme: F: Nervous System Disorders

Modeling psychiatric illness using human iPS cells from a Scottish family.

Ellen Grünewald[1], Paraskevi Makedonopoulou[1], Karen Burr[2], Shyamanga Borooah[2], David Porteous[1], Douglas Blackwood[3], Andrew McIntosh[3], Siddharthan Chandran[2] and Kirsty Millar[1]

[1]MRC Institute of Genetics and Molecular Medicine, University of Edinburgh, [2]MRC Centre for Regenerative Medicine, University of Edinburgh, [3]Division of Psychiatry, University of Edinburgh

Psychiatric illness has a clear genetic component as is clear from twin, family and adoption studies. This study focuses on a large Scottish pedigree in which a balanced translocation between chromosomes 1 and 11 (t(1;11)) co-segregates with schizophrenia, major depressive disorder and bipolar disorder. At the translocation breakpoint lies Disrupted-in-Schizophrenia1 (DISC1), one of the most studied risk genes for mental illness. This gene has subsequently been shown to have key roles in neuronal development, in progenitor proliferation and in migration. We aim to study disease mechanisms underlying the mental illness in this family by generating induced pluripotent stem cells (iPSCs) and investigating neural precursor cells (NPCs) and differentiated forebrain neurons. To this end skin biopsies have been taken from t(1;11) translocation carriers and within-family controls. Using episomal methods we have generated over 30 iPSC lines from 11 individuals of this family. Several lines have been converted into NPCs and differentiated into forebrain neurons. This material has been characterised and used for functional and expression studies. We are particularly interested in the effects of the translocation on neurite outgrowth, progenitor proliferation, cell signaling, mitochondrial function, and transcript and protein expression.

Theme G: Methods and Techniques

Posters P2-G-001 to P2-G-014

Poster Ref: P2-G-001

Theme: G: Methods and Techniques

G2C-SynMAPP: A high-throughput imaging and automated analysis tool for quantifying synapse types in brain tissues.

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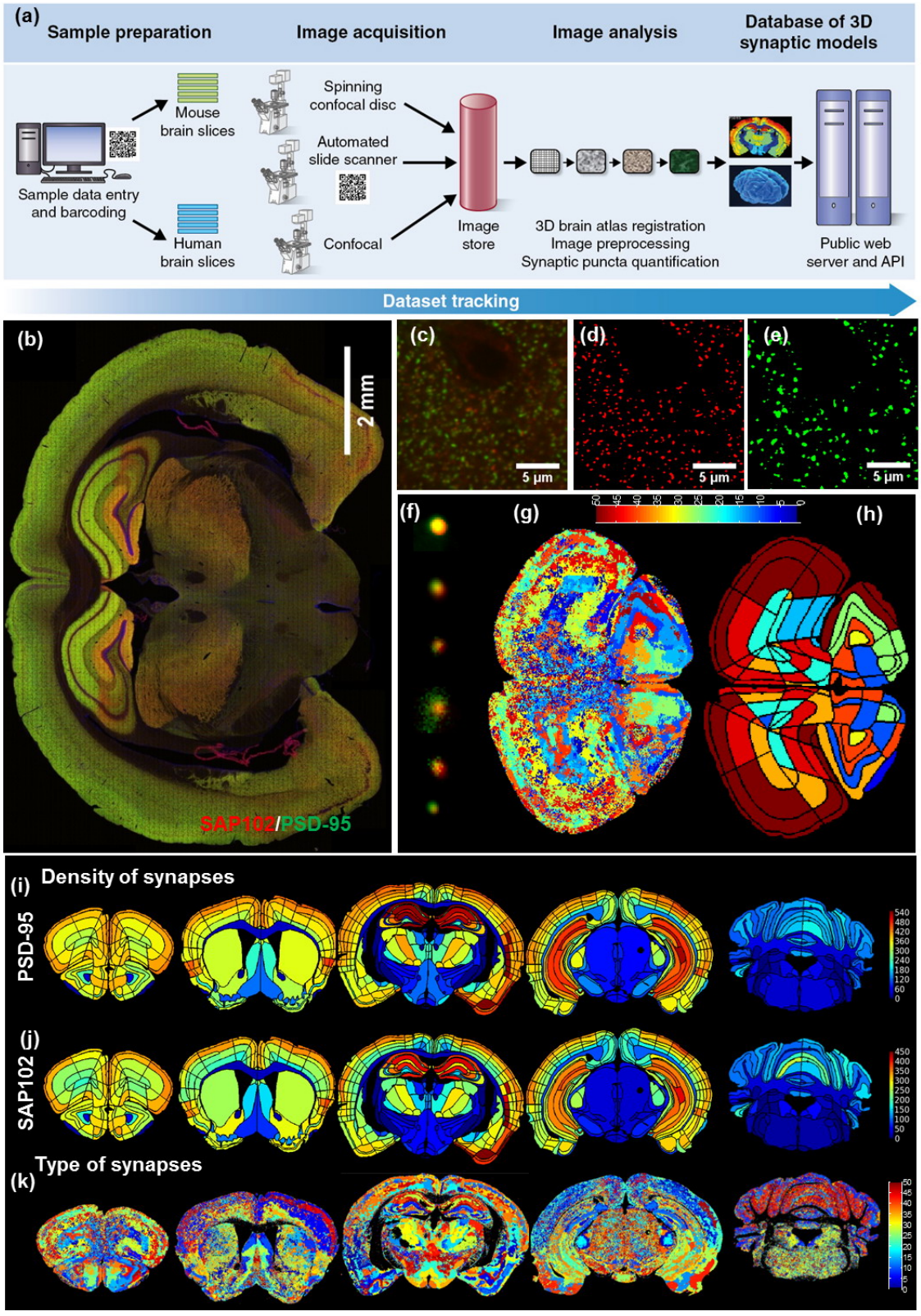
Centre for Clinical Brain Sciences and Centre for Neuroregeneration, University of Edinburgh

Over 130 brain diseases directly involve proteins expressed in synapses[1]. Current methods for analyzing protein expression in single synapses use slow imaging and manual analysis techniques that are not suited for systematic brain-wide studies. There is a pressing need for high-throughput imaging and automated analysis of brain synapses at single synapse resolution at the whole brain scale. We have established a high-throughput and automated imaging analysis pipeline called Genes to Cognition Synaptic MAPping Pipeline (G2CSynMAPP) that can characterize and map diversities of individual synapses either in a whole mouse brain or human brain tissues.

Spinning disk confocal microscopes (SDM) are used for high-throughput (~450Gb/day) and high-resolution (~280 nm) synapse image acquisition from mouse coronal and sagittal sections. Synapses can be labelled with either genetically tagged fluorescent proteins or antibodies (see posters: Zhu *et al.* and Cizeron *et al*). We developed a state-of-the-art algorithm[2] to detect synaptic puncta from fluorescence images and extract visual features of the synaptic proteins, including densities, coordinates, intensities, sizes, shapes, *etc*. Combining labels from multiple synaptic proteins enabled quantitative analysis of colocalization. We utilize deep neural network approaches[3] to hierarchically classify different types of synapses at different levels of visual complexity and spatial resolution in an unsupervised manner based on the features extracted. Finally we map all types and features of synapses into the Allan Brain Institute coordinate system to generate whole brain synaptome maps. We have established that G2CSynMAPP is a powerful technology for mapping the molecular and synaptic organisation of the mouse and human brain and it is useful in detecting synaptic pathology arising from schizophrenia and intellectual disability mutations, Alzheimer's disease and traumatic head injury. Mapping the molecular composition and diversity of synapses will be a new frontier in the study of brain and behaviour.

1. Bayes, A. & Grant, S.G. Nat Rev Neurosci 10, 635-46 (2009);
2. Yang, L., Qiu, Z., Greenaway, A.H. & Lu, W. IEEE Trans Biomed Eng 59, 2040-2050 (2012);
3. Jones, N. Nature 505 (2014).



(a) A diagram of G2CSynMAPP; (b) Montage image (7869 x 5197 pixels) downsampled by 1024 folds from raw SDM data (~1Tb); (c-e) A raw SDM image and the segmented results of SAP102 and PSD-95; (f-h) Synapse classification results at single synapse, image and anatomical region resolutions. (i-k) Heat maps of synapse densities and synapse types coded by different colours across 5 mouse brain sections.

Poster Ref: P2-G-002

Theme: G: Methods and Techniques

A pilot study of potential electrophysiological measures of aging, and Alzheimer's disease, in people with Down's Syndrome.

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Introduction: Down's Syndrome (DS) is a genetic disorder attributed to the triplication of chromosome 21, and is associated with premature aging and an increased risk of developing Alzheimer's disease (AD). AD typically presents with memory decline however some of the earliest clinical indicators of AD in DS are compromised frontal lobe functions, such as inhibitory control. This research project aims to test the potential value of electrophysiological measures: electroencephalography (EEG) and event-related potentials (ERPs), for indexing age-related changes to cognitive functions underpinned by the frontal lobes.

Method: EEG is a method of recording bio-electrical activity generated by cortical neurons and ERPs are the averaged responses to specific stimuli. The ERPs that will be investigated in this project are: P3 which has been repeatedly suggested in the literature to be perturbed in AD; MMN which is maximal over fronto-central sites, thus could reflect activity in a brain region of interest for DS-AD; P50 Suppression which, having been correlated with inhibitory control, could potentially index a cognitive process vulnerable to DS-AD. These relatively inexpensive measures have also been selected to be readily feasible in adults with an intellectual disability, requiring only limited active cooperation and thus could have wide clinical utility.

The electrophysiological measures are gathered using a high-density array EEG net of 129-channels (EGI's HydroCel Geodesic Sensor Net) and recorded onto the NetStation computer program. The ERPs are elicited by auditory stimuli, delivered by the MATLAB plugin Psychtoolbox and presented at a comfortable volume. During the passive P50 suppression task participants watch a silent movie. During the P300 and MMN elicitation participants listen and, only to maintain attention, are asked about repeated patterns of sounds.

The electrophysiological measures will be correlated with cognitive measures sensitive to the progression of AD in DS.

Conclusion: The pilot study aims to test the acceptability and feasibility of these ERPs with 5 adults with DS and 5 age- and gender-matched controls. The optimised paradigms will then be tested with a larger cohort of individuals to assess their potential value in DS-AD research.

Poster Ref: P2-G-003
Theme: G: Methods and Techniques

Exploring the possibility of destroying cholinergic terminals in the rat VTA.

Josephine Fullerton and Philip Winn
University of Strathclyde

Cholinergic input to the ventral tegmental area (VTA) contributes to the rewarding properties of drugs of abuse. The pedunculopontine tegmental & laterodorsal tegmental nuclei (PPTg, LDTg) provide input to VTA dopamine (DA) neurons, but the specific role of cholinergic terminals in the VTA is unclear. Based on mesopontine expression of urotensin II receptors (UII-R) a fusion toxin was developed combining diphtheria toxin and urotensin II (Dtx-UII), forming a selective neurotoxin for mesopontine tegmentum cholinergic neurons. This toxin destroys cholinergic neurons after direct injection into PPTg. However, loss of either PPTg or LDTg only eliminates a proportion of cholinergic input to the VTA. Is it possible to inject Dtx-UII direct into the VTA to destroy all the cholinergic terminals there?

To determine what effect Dtx-UII has on mesopontine cholinergic projections, Dtx-UII (200nL, 3%) was unilaterally infused into posterior VTA (pVTA). Rats were perfused at various times (2, 4, 6, 8 & 10 days) after surgery to determine whether complete denervation of cholinergic input to pVTA can be achieved. Tissue was analysed through fluorescent immunohistochemistry using vesicular acetylcholine transporter (VAChT) which labels cholinergic neurons, and fluoro-jade C, which has strong affinity for degenerating axons, dendrites and terminals. Control experiments were undertaken infusing ibotenate (180nL, 0.06%) into pVTA.

Infusion of Dtx-UII into pVTA Dtx-UII did not alter VAChT expression 2, 4, 6, 8 & 10 days after surgery. There were no detectable immunohistochemical differences observed in VAChT or fluoro-jade C staining; this would indicate that cholinergic terminals remained present in the VTA and that no neurodegeneration occurred. Ibotenate infusion into pVTA produced a marked increase in fluoro-jade C activation. Further experiments could investigate higher concentrations of Dtx-UII: UII-Rs are expressed at a lower level in VTA than PPTg/LDTg. Furthermore, because Dtx-UII is expected to act through retrograde degradation, it may require longer times to initiate cell death. This toxin holds potential to deepen our knowledge of the relationship between the mesopontine tegmental nuclei and VTA, aiding our understanding of addiction.

Poster Ref: P2-G-004

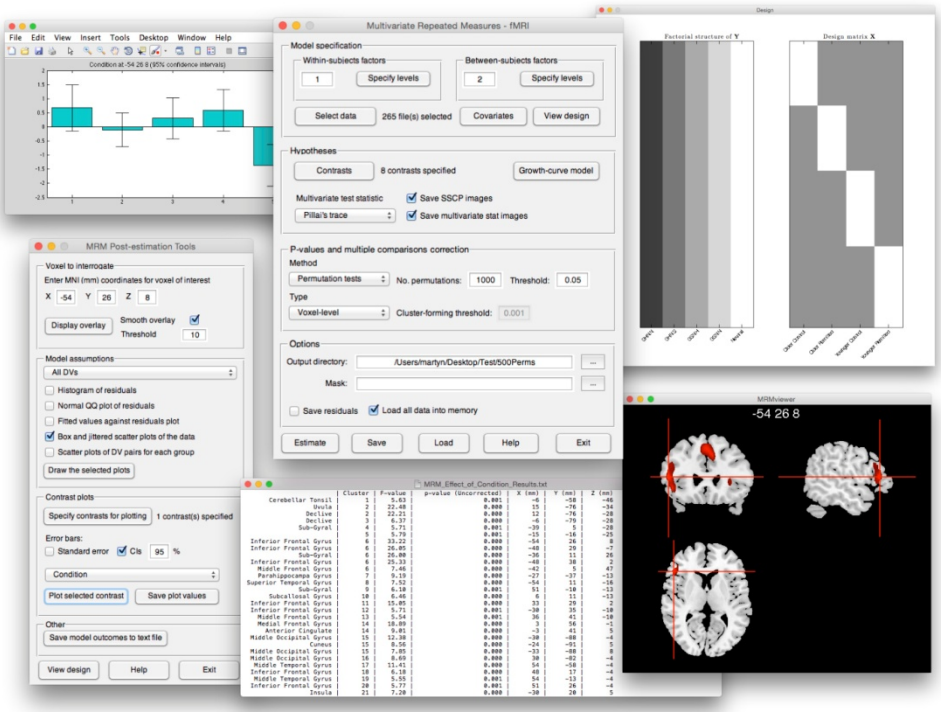
Theme: G: Methods and Techniques

Multivariate modelling of repeated measures and longitudinal neuroimaging data: a new approach and toolbox for group-level fMRI analyses.

Martyn McFarquhar, Shane McKie, Richard Emsley, Rebecca Elliott and Steve Williams

University of Manchester

Both repeated measurement and longitudinal group-level fMRI data are becoming increasingly more common. At present the analysis of these designs poses difficulties for popular software packages. In FSL the within-subject covariance matrices are assumed compound-symmetric, whereas in SPM the same covariance structure is assumed true across all voxels. Further restrictions are imposed by the fact that neither software allows easy specification of different error terms for univariate F-tests, making repeated-measures ANOVA models difficult to implement. A recent spate of interest in improving these approaches has lead to a number of toolboxes specifically designed for longitudinal and repeated-measurements (e.g. GLMFlex, SwE). However, these software packages differ wildly in their user-friendliness and feature-set. Here we present a new approach to modelling dependent fMRI data, and provide a preview of a new user-friendly and feature-rich toolbox implementing this approach. We make use of the multivariate form of the familiar univariate linear model where the repeated-measurements are treated as separate outcome vectors. This allows their individual variances and covariances to be estimated uniquely at every voxel. Contrasts are specified using separate matrices for the within- and between-subject structures, allowing great flexibility in the questions that can be asked. Inference is then performed using F approximations to common multivariate test statistics. Corrections for multiple comparisons available *via* either an FDR or permutation-based FWE approach. Because of this, very few assumptions are necessary for valid inference. Here we present both the theory behind this approach as well as comparisons of results from several current packages. We also present features of the MATLAB-based software that will be available for efficiently fitting these models to fMRI data.



Example of the multivariate repeated measures (MRM) MATLAB toolbox GUIs.

Poster Ref: P2-G-005

Theme: G: Methods and Techniques

A framework for conditional non parametric directionality analysis.

David Halliday[1], Mohd Harizal Senik[2], Michael O'Donoghue[3], Carl Stevenson[4] and Rob Mason[2]

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Directed network analysis is widely used in Neuroscience to infer network structure in multivariate neural recordings. The majority of approaches are parametric, using estimates of parameters from a model to quantify interactions between the observed signals, typically using auto-regressive (AR) models. Once the AR parameters have been estimated different metrics relating to directionality can be constructed directly as a function of the estimated parameters. A recent article introduced a non-parametric framework for directionality analysis of bivariate data (Halliday DM; 2014 In review) Non-parametric directionality measures: Theory and application to spike train data; submitted), with application to simulated and experimental spike train data. Here we extend this framework to include measures of directed conditional independence. The concept of conditional independence is widely used in partial regression models where the effects of variables that are believed to influence the correlation between dependent variables are removed to provide a more accurate description on any dependency. The use of conditional causality measures to distinguish between direct and indirect influences has been considered in parametric approaches to directionality. Granger (Econometrica (1969) 37: 424-438) considers two and three variable models, leading in the three variable case to a partial cross spectrum from which causal and feedback relationships between two variables conditioned on a third can be derived. Here we demonstrate how the bivariate non-parametric framework in Halliday (2014) can be extended to multivariate data by presenting an extension to deal with analysis of three random processes. We also investigate applicability of the framework to time series data as well as spike train data. One advantage of considering time series data is that measures derived from residual and conditional variance metrics can readily be calibrated against known (simulated) data. We undertake such a comparison to establish the accuracy and usefulness of our multivariate extension. The new approach is applied to experimental single unit and local field potential recordings obtained bilaterally in the anaesthetised rat hippocampus.

Poster Ref: P2-G-006

Theme: G: Methods and Techniques

Muscle modelling to estimate muscle forces for upper limb rehabilitation.

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Department of Biomedical Engineering, University of Strathclyde

Stroke is a leading cause of paresis. Paresis significantly affects stroke survivors' quality of life by impeding them from performing activities of daily living. Physical therapy is the mainstay of providing rehabilitation to stroke survivors. Prompt and long term repetitive and intensive physical therapy can improve the symptoms of paresis as it induces cortical reorganization of neurons aiding motor relearning. However, due to the large number of patients on waiting lists, it is practically not feasible for therapists to provide longer duration of physical therapy necessary for complete recovery. Rehabilitation robotics and exoskeletons are devices that may fill in the gap in providing intensive and repetitive physical therapy required to achieve effective therapy in aid of the physiotherapists who will be able to design rehabilitation programmes delivered in giving long-term physical therapy to stroke patients.

We are interested in developing an upper limb exoskeleton for stroke patients' rehabilitation. We believe that it is of paramount importance to have a physiologically oriented control strategy for the exoskeleton device to assist the motion of the body part involved. In this study, we present a muscle modelling technique to estimate torque at elbow joint. This muscle model uses electromyography (EMG) and joint kinematics to predict the joint torque. The model was developed using a modern version of Hill type muscle model. This version has been tested on healthy subjects and the results are comparable to the torque calculated from the motion equations of the upper arm. Predicting accurate joint torque is critical to the operation of the device in giving assistance to the motion of the arm. Moreover, the intended device will enable monitoring improvements in performing tasks by studying the torque patterns during the rehabilitation period. Thus, a practitioner can intervene and alter the rehabilitation programme, if necessary. Only with effective force estimation, a realistic and seamless assistance can be provided to the stroke patients by the exoskeleton device.

Poster Ref: P2-G-007

Theme: G: Methods and Techniques

Efficacy of a training on emotion processing in severe brain injured subjects.

Maria Aiello[1], Valentina Galetto[1,2] and Marina Zettin[1,2]

[1]Puzzle Rehabilitation Center, Turin, Italy, [2]Department of Psychology, University of Turin

Severe traumatic brain injury (TBI) could result in a range of neuropsychological deficits leading to diminished psychosocial functioning. Deficits in social skills have been described as a frequent consequence of traumatic brain injury (TBI) and could be interpreted as a consequence of a primary problem in emotion processing, *i.e.* the ability to adequately perceive and elaborate other people's facial expressions and bodily gestures with emotional meaning. This impairment may give raise to dysfunctional behaviours, leading to significant difficulties in everyday life.

The purpose of this study was to assess the effectiveness of a training aimed at improving emotion processing ability in a group of brain injured subjects.

Eleven severe TBI subjects participated in the study. Before the experiment they were submitted to an evaluation including tests on emotion recognition, alexithymia, depression, anxiety and awareness. The training, lasting three months, was founded on Ben Yishay (1981; 1990) and Prigatano's (2005) statements about neuropsychological rehabilitation. It consisted of two weekly sessions. In the first one the subjects took part to the so called "Hot Seat". Here the protagonist, who was in turn one of the patients, introduced himself (or herself) to the rest of the group. At the end of the presentation, the remaining participants gave him (or her) feedbacks about his (or her) performance, focusing on the emotions they felt. The second part of the treatment consisted of a group aimed at improving participants' ability to express their own feeling and recognize the others' emotional states.

At the end of the treatment TBI subjects were submitted to a second assessment.

Outcomes of the study highlighted an overall improvement in all the analyzed dimensions. However, this amelioration didn't reach the statistical significance. There may be various explanations of such results: first of all, our treatment may not have been enough long-lasting, especially considering the severity of participants' brain damage. Secondly, other factors, such as social context, may have interfered. However, this study is one of the first to investigate the clinical efficacy of a training on emotions in brain damaged subjects, focusing on its impact on everyday life.

Poster Ref: P2-G-008

Theme: G: Methods and Techniques

Diffusion MRI predicts the topographic organisation of visual cortical and sub-cortical areas.

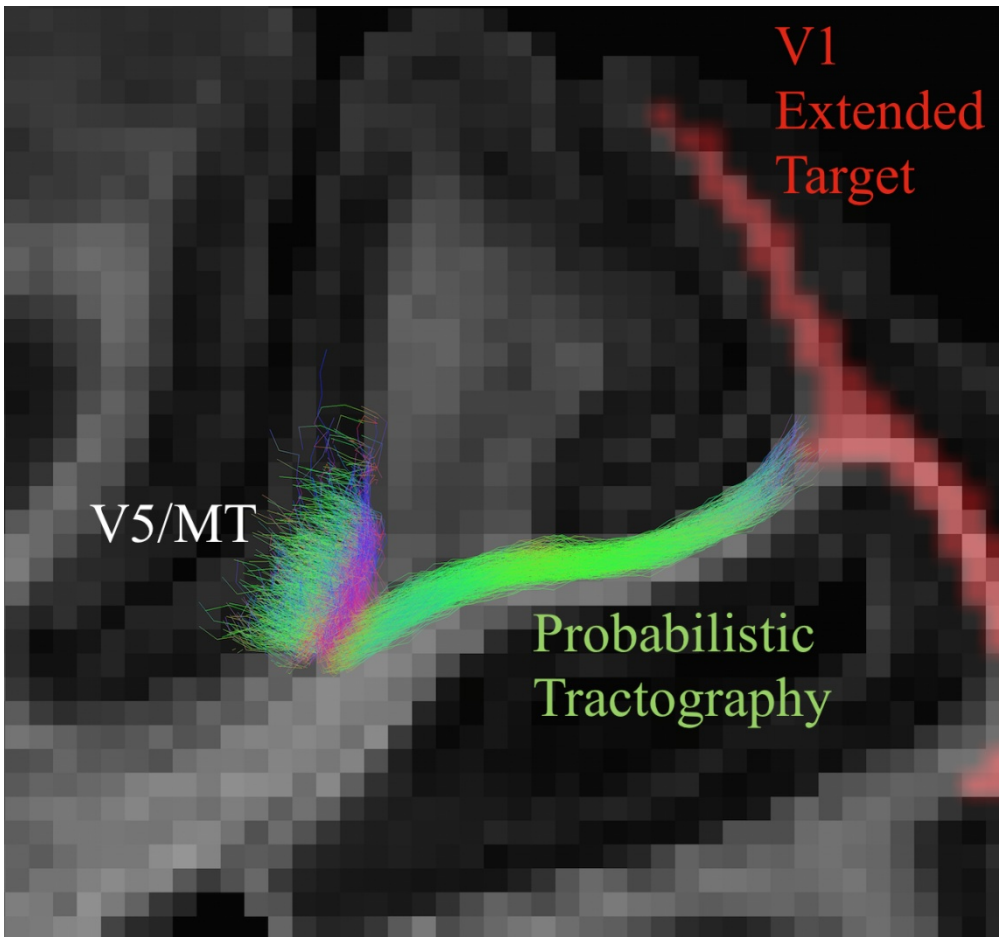
Jackson E. T. Smith[1], Kim-Long Tang-Wright[1], Tim B. Dyrby[2], Holly Bridge[1], Karla Miller[1], Bashir Ahmed[1], Andrew J. Parker[1] and Kristine Krug[1]

[1]University of Oxford, [2]Copenhagen University, Denmark

Clinical use of diffusion MRI (dMRI) is limited by scan times, resolution and signal strength. To test whether clinical-grade dMRI can detect known anatomical connections, we obtained two sets of dMRI from 5 brains (*Macaca mulatta*) and compared these data with each other and against established functional visuotopic maps. One set was taken *in vivo* with a level of voxel resolution and signal strength comparable to human clinical data (3T, 61 gradient directions, b=1000s/mm2, 1mm3 isotropic voxels); another set was taken post-mortem with a higher level of resolution and signal strength (4.7T, 61 directions, b=4300s/mm2, 0.5mm3 isotropic, Dyrby *et al.* 2011).

To test the available resolution of dMRI, we used the visual topographic organisation of the lateral geniculate nucleus (LGN) and visual cortical area V5/MT as a basis for predicting the outcome of probabilistic tractography of the connections from these two sites to primary visual cortex (V1). Anatomical studies have shown that V1 has direct axonal connections to LGN and V5/ MT, and functional visuotopic maps have been established in relation to anatomical landmarks (Van Essen *et al.* 1984, Erwin *et al.* 1999). Tractography was applied to the dMRI data with MRtrix using 0.5mm steps, and sampling from a 120° cone of possible orientations; exclusion masks blocked the sulci, ventricles, and midline. Cortical target masks were extended into well-connected, immediately-adjacent white matter voxels identified from preliminary tractography.

Based on the relative strength of probabilistic connection to central (<10° from fixation) or peripheral (>12°) V1, the receptive-field location was determined for each voxel in LGN and V5/ MT. This technique predicted topographic maps of LGN and V5/MT that were qualitatively correct, in most hemispheres. When comparing topographic maps from the same hemisphere in two animals, all LGN and V5/MT maps from the in-vivo dMRI classified a significant number of voxels the same way as maps from the post-mortem dMRI (mean = 84% voxels, $P < 0.001$, permutation test, Nichols and Holmes 2001). Thus, clinical-grade dMRI can identify more than just the presence of a connection between two cortical areas; it also successfully reveals topographic order in the anatomical projections between areas.



Probabilistic tractography (coloured lines) was used to estimate the connectivity of V5/MT (shown) and LGN to V1 targets that encode different parts of the visual field. Here, the target (red) is a set of white-matter voxels that are well connected and close to central (<10° from fixation) V1. Connectivity estimates were used to predict the visual-field representation of each V5/MT and LGN voxel.

Poster Ref: P2-G-009
Theme: G: Methods and Techniques

Tracking amyloid oligomers *in vitro* and *ex vivo*.

Glynn Jones, David Koss and Bettina Platt
Aberdeen University

Amyloid beta (Aβ) plays a central role in Alzheimer's disease (AD) pathology, but the identity of toxic species contributing to the disease process remains a matter of debate. Further, the relevance of Aβ species formed *via* synthetic aggregation methods has emerged as a key technical concern. Here, we utilised a novel oligomer-specific reporter, L-tryptophanol (Trol) to investigate two issues: 1) Which parameters affect aggregation of synthetic Aβ *in vitro*? 2) Can the reporter detect oligomeric Aβ in mouse brain lysates *ex vivo*?

The reliability of the assay, behaviour over time, and impact of aggregation parameters were determined in 96-wellplates. Synthetic Aβ (12.5 μM) de-aggregated with HFIP was dissolved in either Ca/Mg-free PBS or DMEM F12k. Both conditions were also tested with agitation and results quantified *via* Trol fluorescence readings (100μM, ex:280 nm, em:355 nm) over 4 hrs (Δt=30 min). Mouse brain lysates from 3 transgenic lines (PLB1Triple (knock-in of APP & tau plus PS1 genes), PLB4 (hBACE knock-in) and a APP/PS1 over-expression model) were probed for naturally produced Aβ; results were confirmed *via* western Blots (6E10 and MOAB antibodies).

Synthetic Aβ in PBS reached a plateau within minutes of dissolution (signal quenching -17%), while DMEM treated samples peaked at ~48 hrs (-10%). Signals were stable over time in the presence of Trol. However, a transient increase in fluoresce was observed (+ 7.5%) 60-120 mins after dissolution of Aβ in PBS (in the absence of Trol), indicative of the formation of an additional amyloid species. Agitation, reported to promote fibril formation, abolished the Trol signal quenching in both buffers in a time dependent manner, *i.e.* after 4 hours in PBS and 48 hours in DMEM. Ex vivo testing indicated that the Trol assay was capable of detecting low levels of oligomeric Aβ in brain lysates, and to distinguish between mouse lines dependent upon oligomeric Aβ load, with data corroborated by immuno-blotting results. Further testing in human tissue is now also underway.

Overall, aggregation behaviour of Aβ *in vitro* is severely affected by experimental conditions which are difficult to fully validate. However, Trol is a convenient fluorescence assay for complimentary quantification of Aβ oligomers *in vitro* and *ex vivo.*

Poster Ref: P2-G-010

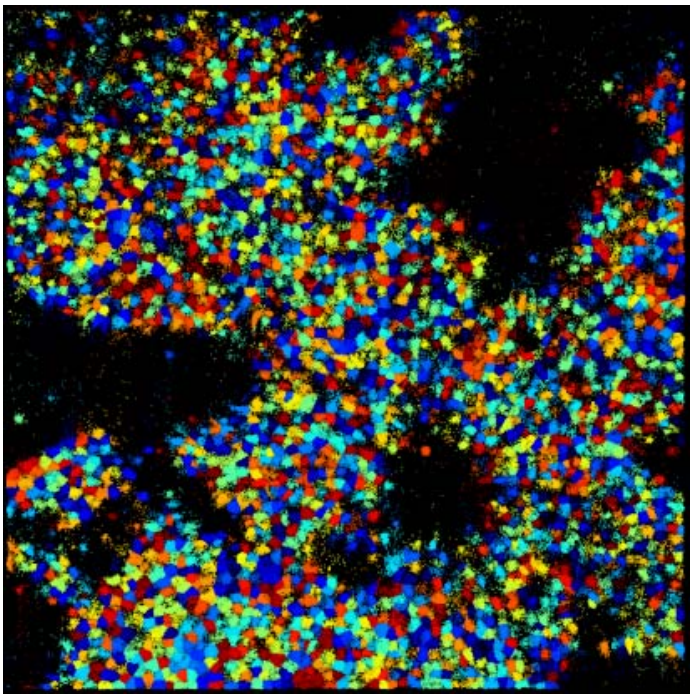
Theme: G: Methods and Techniques

Characterization of very large ganglion cell populations in the mouse retina.

Sahar Pirmoradian[1], Gerrit Hilgen[2], Martino Sorbaro[1], Oliver Muthman[1+3], Upinder Bhalla[3], Evelyne Sernagor[2] and Matthias Hennig[1]

[1]University of Edinburgh, [2]University of Newcastle upon Tyne, [3]Tata Institute of Fundamental Research

Morphological and physiological analyses indicate the retinal population response consists of a number of separate channels, each represented by a different ganglion cell (RGC) type with distinct functional characteristics. To characterize these pathways in more detail, we recorded light responses from the mouse retina with a high-density multi-electrode array with 4096 channels (64x64 channels, pitch 42 µm). This allowed simultaneous monitoring of the activity of thousands of RGCs in about 1/3 of a mature retina. In these recordings, signals from single neurons are typically detectable on multiple, nearby channels. We present a new method to exploit this to improve the signal to noise ratio for spike detection, and to estimate a current source location for each spike. This yields a map of neural activity with much higher spatial resolution than provided by the array, where spikes from individual neurons form dense, isolated clusters. These were separated into single units using Mean Shift clustering. Direct comparison with raw data shows this is a new, highly efficient method for spike sorting requiring minimal manual intervention. We then quantified light responses using full field stimulation and linear models derived from white noise stimulation. Although broadly distributed, response kinetics had a clear dorsoventral gradient: RGCs in more ventral locations responded more slowly, and receptive fields of Off cells were larger in ventral than in dorsal locations. It is unclear whether this specificity reflects varying properties within certain cell classes, as for example receptive field sizes in the primate retina, or different cell classes in different locations. Moreover, unlike in other mammalian species, we found a larger number of On than Off cells. Overall our results demonstrate substantial region specificity and functional specialization in the retina, most likely reflecting ecological requirements.



An example of spike clustering on a mouse retina. Spikes are colored by cluster membership. ~1800 clusters were formed.

Poster Ref: P2-G-011

Theme: G: Methods and Techniques

Conditional neuronal connectivity from multiple electrode array recordings using multivariate partial coherence analysis.

Siti Noormiza Makhtar[1], David Halliday[1], Mohd Harizal Senik[2] and Rob Mason[2]

[1]Department of Electronics, University of York, [2]School of Life Sciences, University of Nottingham

Studying the neuronal pattern of interactions may help us to understand the underlying processes of functional connectivity in the brain. With the emergence of Multiple Electrode Array (MEA) technology for recording high volumes of neuronal signals, appropriate statistical and computational methods of multivariate analysis becomes crucial to demonstrate the interactions between neurons. In this study, a computationally efficient approach to compute higher order partial coherence using ordinary second order spectra will be adapted for MEA spike train data (J. Neurosci. Methods (1997) 77: 93-107 & Metrika (2000) 51: 157-172). The analysis was implemented on simultaneously recorded signals recorded from four different hippocampal regions (left and right CA1 and CA3) in isoflurane-anaesthetized Lister-hooded rats before and after local unilateral kainic acid (KA)-induced epileptiform activity (micro-injection into the left hippocampus only) (Synapse (2008) 62(10): 746-755 & Society for Neuroscience (2013) 143.05). Multivariate partial coherence analysis was conducted on a 300 sec duration epoch of the spike trains to compute the strength of pairwise conditional relationship among neurons. Graphical illustrations of the time-frequency relationships were constructed to compare the patterns of interactions using the ordinary coherence and partial coherence values. Time-frequency analysis was undertaken by analyzing consecutive 300 sec sections. These illustrations provide temporal windows of color-coded coherence and partial coherence values to visualize the strength of neuronal interactions for frequencies from 0 to 100 Hz. Comparison of four different stages (before KA, during KA, after KA - strong effect, after KA - weak effect) of the MEA recording show the effect of KA on neuronal interactions within the same region, as well as across the different regions. These colormap illustrations could be used to distinguish the strength of direct and indirect connectivity which localized in specific frequency bands. This could helped us to gain deeper knowledge about neuronal connectivity within and across the seizure area after locally-induced epileptiform activity.

Poster Ref: P2-G-012

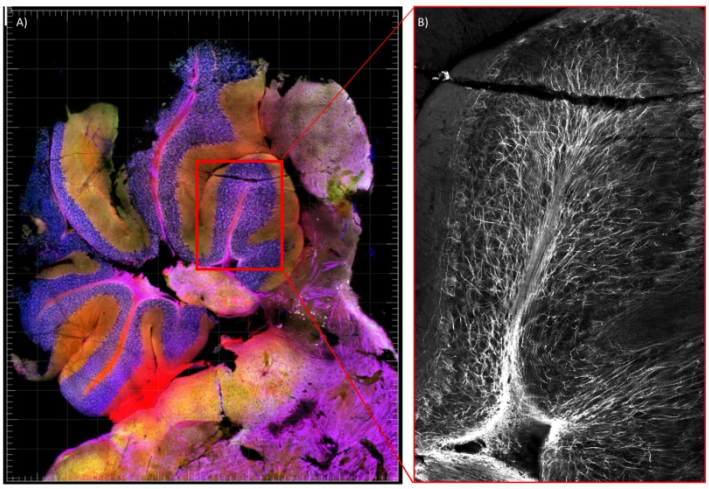
Theme: G: Methods and Techniques

Providing CLARITY to Ataxia in patients with Mitochondrial disease.

Jonathan Phillips, Robert Lightowlers, Doug Turnbull and Nichola Lax

Wellcome Trust Centre for Mitochondrial Research, Newcastle University

Mitochondria are essential organelles of the cell as they generate the majority of the cells energy in the form of adenosine triphosphate (ATP). Mitochondria are unique organelles in that they contain their own DNA (mtDNA) encoding proteins essential for oxidative phosphorylation (OXPHOS), the process that drives ATP generation. MtDNA mutations result in dysfunctional mitochondria due to impaired OXPHOS. Impaired OXPHOS has the greatest impact on the tissues with a large energy demand, such as brain and muscle. Neurological symptoms are very prominent in patients with mitochondrial disease, especially cerebellar ataxia. Cerebellar ataxia is observed in 68% of mitochondrial disease patients and is associated with a loss of co-ordination, impaired balance, speech difficulties. To elucidate the mechanisms that cause ataxia in mitochondrial disease patients, proteins associated with mitochondrial function and neuronal structure were investigated using immunofluorescence. The major limitation with current immunofluorescent techniques is that only very thin sections (7μm) can be used, as lipids in the tissue causes the light emitted from the fluorescent dyes to scatter, reducing the resolution of the image. In order to use thicker sections (~500 μm), a novel technique known as CLARITY (Clear, Lipid-exchanged, Acrylamide-hybridized Rigid, Imaging/immunostaining compatible, Tissue hYdrogel) is being optimised. CLARITY works on the principle of removing the lipids from the tissue that would otherwise scatter the light while simultaneously retaining the proteins and DNA by hydrogel embedding. CLARITY will enable subtle differences in the cerebellum of mitochondrial disease patients to be observed compared to controls. Particular changes include Purkinje cell morphology abnormalities, Purkinje cell connectivity and distribution of dysfunctional mitochondria within individual Purkinje cells. In addition to human tissue, CLARITY will be applied to mouse models of mitochondrial disease, allowing us to investigate the progression of neurodegeneration, something that is not possible in humans. Applying CLARITY to tissue from mice and humans will allow us to further understand the mechanisms of Purkinje cell death in patients with mitochondrial disease.



A tiled image of a 500μm thick section of mouse cerebellum that has undergone CLARITY. A) The section has been stained for nuclei (blue), mitochondria (green), Neurofilament H (red) and Myelin Basic Protein (magenta). B) A black and white image of myelin basic protein in one of the cerebellar folia. The complex network of axons entering the white matter is clearly visible.

Poster Ref: P2-G-013
Theme: G: Methods and Techniques

StereoMate: automated stereological analysis of synaptic puncta using confocal microscopy and image deconvolution.

Steven J. West and David Bennett
University of Oxford

Neural connectivity plays an important role in determining the flow of information within the CNS, yet obtaining a complete map of connectivity is beyond our current capabilities. In an attempt to bridge this gap, we have developed a tractable method for examining connectivity by marking and analysing synapses within the CNS.

Methods: Synapse Staining: Spinal cord was 4% PFA perfused, post-fixed overnight at 4C. Sections were stained for PSD95 and Synaptophysin with different antigen retrieval methods: Heat-induced epitope retrieval (HIER), and protease treatments (proteinase K and pepsin).

Confocal Deconvolution: We used Parallel Iterative Deconvolution (FIJI Plugin), and PSFs were made in PSF Lab (OneMolecule Group). Imaging & deconvolution of fluorescent beads was performed under identical conditions as synapses (TetraSpeck beads, Invitrogen).

Stereology: After image thresholding, we applied our novel automated stereological method (ROI di-sector) and compared it to the manual optical di-sector.

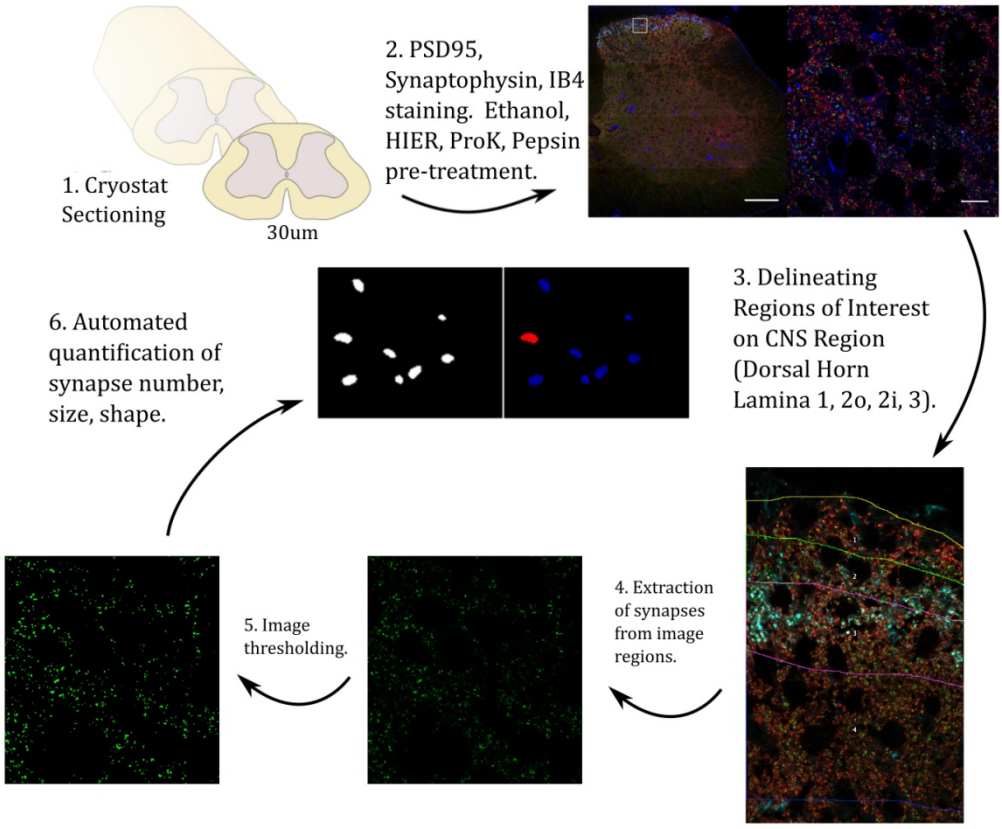
Workflow Application: We analysed a set of PSD95:Synaptophysin synaptic puncta in lamina 1-3 of the dorsal horn spinal cord. Dorsal horn sections from naive rats (Sprague Dawley) and a rhizotomy surgery group (severing peripheral input into the dorsal horn) were analysed.

Results: HIER with protease treatments gave consistent & strong staining. Pre-treatment with HIER showed a significant increase in antibody penetration relative to no HIER pre-treatment.

Deconvolution of fluorescent bead images showed a significant improvement in resolution. The automated ROI di-sector showed no differences in object counts compared to the optical di-sector, but improved speed & consistency, and more detailed analysis of each object was obtained with the ROI di-sector.

Naive dorsal horn analysis of PSD95:Synaptophysin puncta showed significantly increased excitatory synapses within lamina 2 inner. Analysis of rhizotomy-treated dorsal horn showed a significant reduction in excitatory synapses in all laminae.

We present a workflow for the staining, image processing & analysis of synaptic puncta, to produce a realistic representation of synaptic puncta within the CNS. We reliably detect changes in synapse number within the CNS. StereoMate is being packaged into Java for use in ImageJ.



Overview of image workflow. 1: Dorsal horn sections cut at 30um. 2: Dorsal horn was stained with PSD95 and Synaptophysin, and IB4 to mark lamina 2. 3: Different lamina are delineated using the IB4 marker. 4: Synapses are extracted from each region of interest. 5: Synapses are thresholded. 6: Binary images of synapses are quantified – giving rich dataset of synapse number, size and shape measures.

Poster Ref: P2-G-014

Theme: G: Methods and Techniques

Efficient reduced computational neuronal model with dopamine synthesis and release for rapid testing of pharmacological and genetic effects.

Maell Cullen[1,2] and KongFatt Wong-Lin[2]

[1]Altran, Bath, [2]Computational Neuroscience Research Team, Intelligent Systems Research Centre, University of Ulster

Dopamine (DA) is an important physiological component for behavioural learning. Dysfunctions in the dopaminergic (DA) systems have been attributed to cognitive dysfunctions, addictions, psychiatric disorders such as schizophrenia, depression, anxiety disorder and attention deficit hyperactivity disorder, and neurological disorders such as Parkinson's disease. Pharmacological treatments have typically targeted the DA transporters (DAT), DA receptors, Levodopa (L-Dopa), and L-monoamine oxidases (MAO). Variations in DAT and tyrosine hydroxylase (TH) activities due to genetic polymorphisms have also been found. Despite these various studies, an integrated understanding of these mechanisms, and their relationships with dopamine neuronal activity, remain unclear.

In this work, we developed a computationally efficient dopamine neuronal model consistent with neurophysiology, and incorporated it into our previously reduced computational model of dopamine synthesis and release. Specifically, our integrated model provides fast computational testing of the effects of blood tyrosine (from food intake), DAT, L-Dopa, MAO activities, and extracellular DA release. In particular, this is the first model to explicitly incorporate the inhibitory current of DA (D2) autoreceptors and their simultaneous effects on TH and dopaminergic neuronal excitability. Since D2 receptors have been the target of several drugs including antipsychotic drugs, our model can simulate the effects D2 receptor agonists/antagonists or their desensitization.

Overall, our computationally efficient integrated neural model is particularly well-suited for large-scale computational simulations to provide systemic evaluation and prediction of pharmacological and genetic effects.

Poster Session 3
Presented Tuesday 14 April 2015
Posters P3-A-001 to P3-G-014

Theme A: Development
Posters P3-A-001 to P3-A-021

Theme B: Molecular, Cellular and Synaptic Mechanisms
Posters P3-B-001 to P3-B-043

Theme C: Sensory and Motor Systems
Posters P3-C-001 to P3-C-030

Theme D: Learning, Memory and Cognition
Posters P3-D-001 to P3-D-060

Theme E: Sleep, Circadian and Neuroendocrine Mechanisms
Posters P3-E-001 to P3-E-017

Theme F: Nervous System Disorders
Posters P3-F-001 to P3-F-058

Theme G: Methods and Techniques
Posters P3-G-001 to P3-G-014

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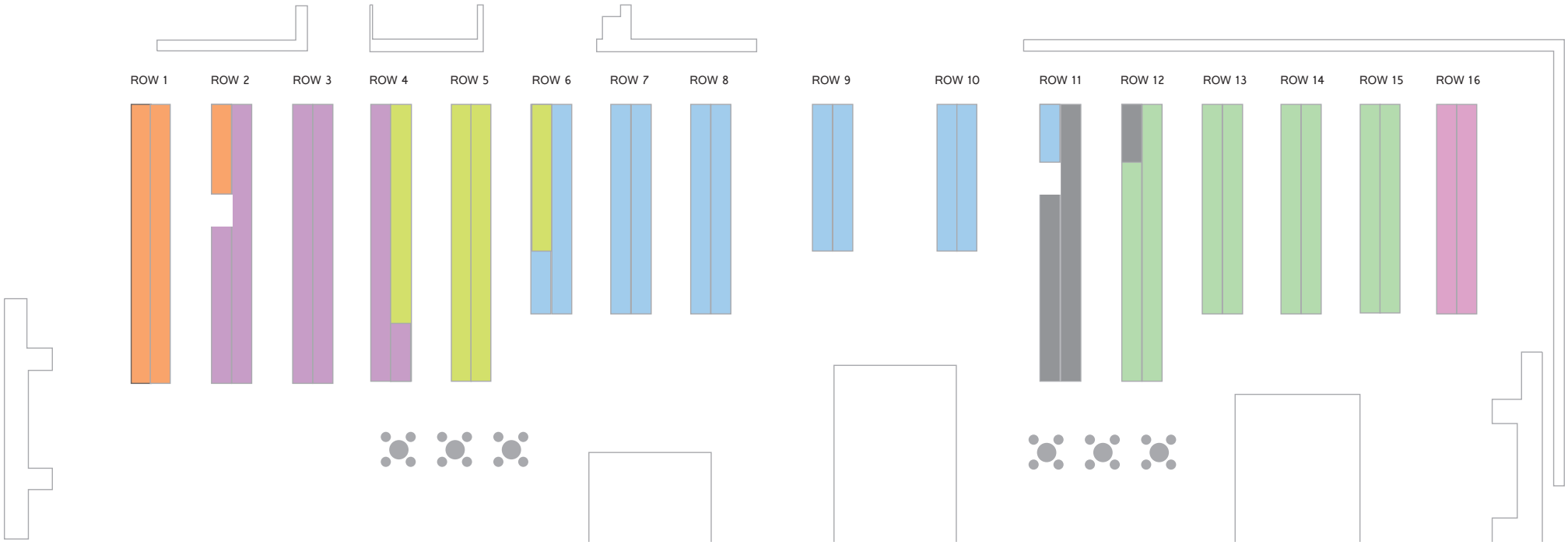
TUESDAY 14 APRIL



- A: Development
- B: Molecular, Cellular and Synaptic Mechanisms
- C: Sensory and Motor Systems
- D: Learning, Memory and Cognition
- E: Sleep, Circadian and Neuroendocrine Mechanisms
- F: Nervous System Disorders
- G: Methods and Techniques
- H: Autonomic Nervous System

Theme A: Development

Posters P3-A-001 to P3-A-021

Poster Ref: P3-A-001

Theme: A: Development

Effects of advanced paternal age on trajectories of social behaviour and motor development in offspring.

Magdalena Janecka[1], Antonia Manduca[2], Servadio Michela[2], Trezza Viviana[2], Rebecca Smith[1], Jonathan Mill[1,3], Leonard Schalkwyk[1,4], Avi Reichenberg[1,5] and Catherine Fernandes[1]

[1]King's College London, [2]Roma Tre University, Italy [3]University of Exeter Medical School, [4]University of Essex, [5]Icahn School of Medicine at Mount Sinai, USA

Advanced paternal age (APA) has been reliably linked to a host of adverse outcomes in offspring, ranging from congenital spontaneous conditions to complex disorders like schizophrenia and autism. Previous studies reported deficits in several behavioural domains in the mouse models of APA, but not their developmental trajectory; also, they failed to show unequivocally that these effects arise de novo in offspring, rather than are parentally-inherited.

Given the strong epidemiological association between advanced paternal age (APA) and sexually-dimorphic neurodevelopmental disorders that are characterized by abnormalities in social behaviour (autism, schizophrenia), we assessed sociability in male and female inbred mice (C57BL/6J) across postnatal development (N = 104) in relation to paternal age. Three groups of offspring of (i) young (8 weeks old fathers), (ii) old (40 week old fathers) and (iii) very old fathers (48 week old fathers) were tested through a battery of behavioural tasks. The tests assessed both early development (emergence of critical reflexes, motor and physical landmarks, and social development), and behaviour in adulthood, focusing on motor and social domains. Majority of the tests run on adult offspring also were run on fathers, in order to eliminate paternal effects that were not related to the father's age at conception.

We found differences in early motor performance and social behaviour in both male and female offspring of older breeders, with adulthood persistence of these effects in males only. We showed that these social deficits were not present in the fathers of these offspring, confirming a *de novo* origin of an altered social trajectory in the offspring generation. Our study is the first investigation of the effects of APA on the developmental trajectory of behaviour in rodent offspring, providing evidence for a causal link between APA, age-related changes in the paternal sperm DNA and neurodevelopmental disorders in their offspring.

Poster Ref: P3-A-002

Theme: A: Development

Formation of motor nuclei depends on an interplay between spontaneous activity, type II cadherins and gap junctions.

Karli Montague[1], Chiraag Thakrar[1], Ana Uzqiano[1], Marc Astick[2], Stephen Price[2] and Sarah Guthrie[1]

[1]MRC Centre for Developmental Neurobiology, King's College London, [2]Department of Cell and Developmental Biology, University College London

Cranial motor neurons cluster together in functional groups termed nuclei. Using the facial and abducens motor nuclei in the avian hindbrain as our model, we have previously shown that during nucleus formation (nucleogenesis), motor nuclei express distinct combinations of type II cadherins, and that manipulating cadherin expression *in vivo* disrupts motor nucleus segregation. We now investigate the roles played by cadherin expression, gap junctions and spontaneous electrical activity in nucleogenesis. We have used the genetically-encoded calcium indicator GCaMP3 to characterise patterns of spontaneous activity among facial and abducens motor neurons during nucleogenesis in the chick brainstem. We find that neurons within a nucleus exhibit synchronised patterns of calcium transients from embryonic day 5 (E5) to E7. We also find that the gap junction protein connexin 43 (Cx43) is expressed by brainstem motor neurons, raising the possibility that gap junctions co-ordinate spontaneous activity. Manipulations of cadherin or gap junction function lead to a loss of synchronised activity, whereas chronic inhibition of activity disrupts cadherin expression refinement and nucleogenesis. This suggests the presence of feedback mechanisms whereby activity serves to stabilise and maintain molecular expression among cranial motor nuclei during development. *In vitro* experiments further suggest a reciprocal relationship in the regulation of type II cadherins and connexin 43. Ectopic expression of cadherin 20 in NIH-3T3 cells results in an increase in Cx43 immunoreactivity at cell-cell junctions, whereas downregulation of cadherin expression decreases Cx43 immunoreactivity. Conversely, knocking down Cx43 expression causes a redistribution of cadherin 11, a type II cadherin. Taken together, the findings of this study suggests the presence of a network of interactions between cadherins, gap junction coupling and spontaneous activity, that presages the emergence of functional properties and cranial motor neuron circuit formation.

Poster Ref: P3-A-003

Theme: A: Development

The ciliopathic gene ARL13B affects cell migration independently of chemotaxic cues and is involved in cell cycle progression.

Michal Pruski, Bing Lang, Colin McCaig and Ann Rajnicek

University of Aberdeen

ARL13B is as a key gene involved in Joubert Syndrome, a disease characterised by retinopathy, kidney disease, mental retardation and cerebellar hypoplasia. ARL13B localises to the primary cilium and although it's exact role remains elusive it is likely to be involved in the processes of initiating cilia formation. This small GTP-ase has previously been implemented in interneuron migration, glial scaffold formation and neural tube patterning. Previous research has emphasised the role of cilia as antennae amplifying developmental signals. Since the hennin (HNN) genotype of ARL13B used in most research is characterised by a shortened cilium it has been thought that ciliary deficits are caused by an inability of the cell to detect those signals appropriately. Here the HNN cells migration and proliferation are further assessed to try to pin point the mechanisms responsible for those deficits.

Direct current electric fields (EFs) have been shown to be present in a wide variety of biological processes including embryonic development, wound healing and neuroblast migration in the adult brain. EF induced migration is thought to not be explicitly initiated by the activation of a specific receptor, but rather to be caused by establishing a cellular gradient of receptors and signalling molecules. By using EFs we have shown that HNN cells display migratory deficits and that are not related to the primary cilia's function in detecting chemotaxic cues, suggesting that there is a more fundamental interaction between primary cilia and migratory mechanisms.

Another key aspect of development that is affected in HNN cells is the cell cycle. The cells divide more slowly and flow cytometry revealed a lower proportion of cells in the S phase and an increased number of cells in the G2/M phase. Western blot analysis has further indicated altered expression levels of SUFU, ERK and the ratio of glu-tubulin and tyr-tubulin.

The data suggests the existence of a key mechanism stabilising the cell and preventing it from migrating and dividing appropriately that is related to the primary cilium.

Poster Ref: P3-A-004

Theme: A: Development

Celsr3 and Frizzled3 control the extension of spinal motor axons in the dorsal hindlimb.

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The atypical cadherin Celsr3 regulates the directional growth and targeting of axons in the central nervous system, but whether it acts in collaboration with or in parallel to other guidance cues is unknown. Furthermore, the function of Celsr3 in the peripheral nervous system is still largely unexplored. Here we show that Celsr3 mediates the pathfinding of motor axons innervating the hindlimb. Celsr3 is expressed in all postmitotic neurons in the spinal cord and dorsal root ganglion neurons. Specific inactivation of Celsr3 in motor neurons leads to a stiff hindlimb phenotype with defective innervation. Celsr3-deficient axons of the peroneal nerve segregate from those of the tibial nerve but fail to extend dorsally, and they stall near the branch point. Mutant axons still respond to the repulsive ephrinA-EphA forward signaling and glial cell–derived neurotrophic factor (GDNF) signaling. However, they are insensitive to the attractive EphA-ephrinA reverse signaling in both neurite outgrowth assay and axon turning assay. In transfected cells, Celsr3 immunoprecipitates with ephrinA2, ephrinA5, Ret, GDNF family receptor α1 (GFRα1) and Frizzled3 (Fzd3). The function of Celsr3 is Fzd3 dependent but Vangl2 independent. Thus, our results show that Celsr3 and Fzd3 interact in motor neurons to cooperatively direct axon growth to target muscles in the dorsal hindlimb. In addition, we provide evidence that the Celsr3-Fzd3 pathway interacts with EphA-ephrinA reverse signaling to guide motor axons in the hindlimb.

Poster Ref: P3-A-005
Theme: A: Development

The expression of autism susceptibility genes in the earliest stages of human cerebral cortex development.

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Neurexins (NRXN) and Neuroligins (NLGN) have established roles in linking pre and post synaptic membranes. Their interactions and the successive recruitment of synaptic density proteins, such as SH3 and multiple ankyrin repeat domains (SHANK), to synaptic membranes influences both synaptic formation and plasticity which in turn shapes neural networks.

Human fetal brains were obtained from the Human Developmental Biology Resource (www.hdbr.org) with appropriate ethical and maternal consents. Quantitative PCR confirmed expression of NRXN, NLGN and SHANK genes from 8-12 post-conceptional weeks (PCW). Of these, NRXN1 and NLGN1 expression was highest relative to reference genes and their expression increased over time. Conversely SHANKs 1-3 expression levels were low and did not increase with age. NRXN1 expression was significantly higher ($p<0.05$) in the anterior cortical region compared to the mid-dorsal, temporal and posterior cortices at 12 PCW.

Immunoreactivity for the synaptic vesicle protein synaptophysin was seen only in the subplate and marginal zones of the cortex from 8 PCW. Immuno-positive staining of NRXN2 was also visible in these synaptic regions. NRXN1 and NRXN3 both showed immuno-positive staining in cells of the post-mitotic cortical plate (CP), migratory cells of the intermediate zone, as well as in the undifferentiated cells of the proliferative ventricular and subventricular layers.
Regulator of NRXN expression, Topoisomerase2β (TOP2β) was expressed in both proliferating and post mitotic cells whilst splicing regulators SLM1 and 2 were confined to the post mitotic CP.

The high expression values of NRXNs in the cerebral cortex and the fact that these proteins do not appear to be confined to the sites of synaptic development suggests functions outside of synaptogenesis at these early developmental stages. The distribution of NRXN protein within the human forebrain at 8-12PCW suggests that NRXNs could be involved in a diversity of functions ranging from controlling cell proliferation to cell differentiation. Proteins controlling the transcription and splicing of NRXNs in adult tissue may have the same functions during early development due to their overlapping expression patterns.

Poster Ref: P3-A-006

Theme: A: Development

Observations on developmental transition profiles of human brain globin transcripts.

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Human globin genes are organized in a β-like closed chromatin domain cluster and an α-like open chromatin domain cluster. In a preliminary RNA-Seq analysis of human brain RNA, we determined massive fetal brain γ-and α-globin read counts which, in the adult brain, were either completely suppressed (γ-globin) or expressed in a limited number (α-globin). Furthermore, considerable abundance of β-globin was detected which, in the fetal stage, was about twice its level of expression in adult brain. Our RNA-seq results also demonstrated minimal expression of both θ and ε globin transcripts in both fetal and adult human brains. Additionally, our preliminary results also suggest brain expression of partial-length transcript fragments of both γ-globin and α- globin genes. The results are now being verified by other molecular techniques. We speculate that the observed developmental patterns of transitions of globin chains in human brain represent adaptive responses to the switching from the physiologically hypoxic embryonic/fetal environment to postnatal normoxia.

Poster Ref: P3-A-007

Theme: A: Development

The Valproate (VPA) rat model of Autistic Spectrum Disorder (ASD): can changes in neural gut innervation provide new insight into aetiology?

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Autistic spectrum disorder (ASD) is a neurodevelopmental condition that affects central and peripheral neurodevelopment, neurochemistry and behaviour. Current aetiological understanding is limited, although the heterogeneity within patient cohorts supports a complex interaction of genetic and environmental mechanisms. Recently, focus has been given to the role of environmental risk factors for ASD (Goyal and Miyan 2014). Maternal insults during pregnancy have been explored using valproate (VPA) administration. VPA exposure has been associated with a higher incidence of ASD in humans and ASD-like behaviours in rodent offspring. Considering the incidence of co-morbid gastrointestinal (GI) dysfunction in ASD patients, particular interest is placed on changes to the neuro-immune circuitry of the GI system in these animal models.

Pregnant Wistar rats were treated with 500mg/kg VPA on gestational day (GD) 12. In a preliminary study, we used anti beta-tubulin staining on the GI tract to quantify the number of nerve fibres innervating the gut. In male offspring at post-natal day 80, a trend was found of increased nerve fibre staining within the small intestine while neural innervation to the large intestine measured in mucosa and muscle was significantly increased in VPA vs. control rats ($p=<0.05$). Interestingly the extent of increased nerve staining positively correlated with the behavioural abnormalities shown in these animals. We also found that the composition of gut microbiota was different in some of the VPA treated rats compared to control which supports previous findings. Metagenomic sequencing of faecal samples from these animals revealed a significant decrease within the acidobacteria phylum in VPA treated rats vs. control ($p<0.01$).

The data suggests that a prenatal exposure to VPA may increase the innervation to the GI tract which is correlated with effects on the GI bacterial environment. Increased nervous supply may provide abnormal sensitivity and feedback from the gut to the brain, resulting in the aberrant behaviour in ASD.

Goyal, D. K. and J. A. Miyan (2014). "Neuro-immune abnormalities in autism and their relationship with the environment: a variable insult model for autism." Front Endocrinol (Lausanne) 5: 29.

Poster Ref: P3-A-008

Theme: A: Development

Chronic exposure to 5HT and 5HT1 agonist 8-OH-DPAT affects development of rat cortical neurons in cell culture.

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Serotonin (5HT) has long been associated with various pathopsychological conditions including depression, schizophrenia and autism. However, its precise role in these conditions is still rather unclear. Interestingly, serotoninergic innervation of the cortex and the expression of 5HT receptors occurs at an early stage during development. In rodents, disturbing 5HT signalling either pharmacologically or genetically during the prenatal or early postnatal period has been shown to affect the morphology and organisation of the cerebral cortex and result in behavioural changes, indicating a link between 5HT signalling and cortical development. However, it is unclear whether these effects are directly mediated by 5HT receptor expression on cortical neurons or the consequence of indirect 5HT actions. For example, 5HT signalling *via* 5HT1B receptors affects the projection pattern of thalamo-cortical axons in the somatosensory cortex. These changes in thalamo-cortical axons affect whisker barrel formation and the morphology of principal layer IV pyramidal neurons and spiny stellate cells. Similarly, reelin secretion from transient Cajal-Retzius cells found in the developing cortex has been shown to be controlled by 5HT and affect cortical cytoarchitecture.

Here we used primary cultures of rat cortical neurons to study the direct effects of 5HT and the 5HT1A agonist 8-OH-DPAT on dendrite growth and synapse formation. Using immuncytochemical staining for the dendritic marker MAP2, we noted changes in dendrite growth of 14 days old cortical cultures that were exposed to either 5HT or 8-OH-DPAT for 10 days. Interestingly, 8-OH-DPAT appeared to have differential effects on dendrite growth of cortical cultures prepared from different rat strains, promoting growth in cultures prepared from Wistar rats, but suppressing dendrite growth in Sprague-Dawley rats. The changes in dendrite growth appear to be associated with changes in synapse formation. Our data suggest that 5HT receptors expressed on cortical neurons can play a critical role in the development of the cortex. The intriguing observation that these effects appear to be rat strain specific could be contributing to behavioural differences between Wistar and Sprague-Dawley rats.

Poster Ref: P3-A-009

Theme: A: Development

Explaining variation in schizophrenia endophenotypes *via* epistasis.

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Many studies have successfully shown a polygenic component explains a significant amount of variation in endophenotypes for schizophrenia. Epistasis is frequently overlooked, but may also play an important role. My recent work has examined variation in cognitive endophenotypes for schizophrenia explained by (1) epistasis in the ZNF804A pathway in working memory above the contribution of the polygenic score (PS) and (2) epistasis between genes annotated by the Mouse Genome Informatics abnormal behaviour phenotype using machine learning algorithms.

Psychosis patients from the WTCCC2 were assessed in cognitive function impaired in schizophrenia (*e.g.*, IQ). For the ZNF804A (1) study, the PS was created using the PGC1 schizophrenia case-control study. In the abnormal behaviour (2) study, the median variable importance measure across 500 runs of the Random Forest algorithm was used to rank SNPs. The top 30 SNPs were tested for interactions using linear regression.

In the ZNF804A study (1) increased PS were associated with poorer performance on endophenotypes. The variation explained (R2) by the PS ranged between 1-3%, which is similar to that observed in other studies. Using a newly-developed statistical model that simultaneously models both polygenic and epistatic components, epistasis in the ZNF804A pathway was found to explain 2-3 times more variability in working memory than the PS. This increase was replicated in two independent samples, including a “narrow psychosis” ($p = 0.016$) and “broad psychosis” set ($p = 0.036$) as well as combined psychosis ($p = 0.0012$). In the abnormal behaviour (2) study, a significant interaction was observed between DISC1 and FOXP2 ($R2 = 1.8$, $p = 0.0083$) and a 3-way interaction with the addition of TUBA1A increased the R2 to 3.6 ($p = 0.0062$). These findings were replicated in the NIMH/Lieber Sibling Study, with the DISC1-FOXP2 interaction explaining (R2) 1.9% of variation ($p = 0.037$), and the 3-way interaction explaining 4.7% ($p = 0.024$).

We show replicated epistasis can explain a significant amount of variation in schizophrenia endophenotypes, and provide both a standard generalised linear model approach and a machine learning method to apply to high-dimensional data to reliably detect epistasis.

Poster Ref: P3-A-010

Theme: A: Development

Dynamic face processing: neural activation differences in empathy, reward and attribution areas in autism spectrum conditions pre and post attribution of emotion.

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Background: Atypical emotion attribution from facial expressions in ASD has been widely reported. A novel dynamic facial expressions paradigm (DFEP) was developed to elucidate the neural processes engaged pre- and post-attribution of emotion from developing naturalistic facial expressions.

Methods: Twenty 8-18 year-olds with ASD and 15 matched TD controls watched 10sec displays of dynamic faces inside an MRI scanner. Subjects pressed a button once they “were sure” that the face, which started with a neutral expression, was expressing happiness, sadness or remaining neutral. Subjects completed 2 runs, each containing 16 blocks of each emotion.

Subject specific design files that split each display into a pre- and post-decision phase (DP) were created, giving a 2 (group) by 3 (emotion) by 2(DP) design. BOLD activation was compared using a 2 x 3 x 2 random effects ANCOVA, with age and VIQ entered as covariates. Main effects and interactions were thresholded at $p < 0.005$, corrected for multiple comparisons using cluster size threshold estimation.

Results: Main effect of Group in the Post-Central Gyrus (PCG), with BOLD activity being higher in the ASD than the TD group. A Group x DP interaction was found in the Caudate, driven by increased activation post- relative to pre-decision in the TD group but not in the ASD group. A Group x Emotion interaction was found in the Supra-Marginal Gyrus (SMG). A complex 3-way interaction in the left Middle Frontal Gyrus (MFG) driven by differences between the groups and emotions in the post-DP.

Conclusions: The ASD group had significantly greater PCG activation than the TD group across all emotions, before and after emotion attribution. Individuals with ASD did not demonstrate increased caudate activation after their decision supporting reduced activation to social stimuli in reward areas of the brain in.ASD. The SMG activation pattern in TD and ASD subjects, suggested SMG engagement may subserve processing of different emotions in the ASD and TD groups. The left MFG activation differences between groups across emotions post decision suggests that this area, which is involved in emotion attribution and empathy, is typically activated pre and atypically activated after the attribution of emotion in individuals with ASD.

Poster Ref: P3-A-012
Theme: A: Development

Evaluating the KappaNEURON hybrid molecular-electrophysiological simulator using models of LTP and LTD.

David Sterratt, Oksana Sorokina and J Douglas Armstrong
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Long term potentiation (LTP) and long term depression (LTD) depend on interactions between ion channels and receptors, influx and diffusion of ions, and binding between and movement of proteins in the synaptic proteome. There are a number of detailed kinetic computational models of parts of the post-synaptic density (PSD), including interactions between subsets of calcium, calmodulin, CaMKII, calcineurin, PP1, neurogranin, SAP97, stargazin and PSD-95. The models are deterministic, simulated by solving ordinary differential equations (*e.g.* Zhabotinsky *et al.* 2006), or stochastic, simulated using Gillespie's stochastic simulation algorithm (*e.g.* Zeng & Holmes 2010). Stochastic simulations can lead to very variable outcomes, even when only a few types of molecule are involved (Zeng & Holmes 2010).

One challenge in building such models is the combinatorially large number of multiprotein complexes that can arise during a simulation, which require an infeasible number of conventional kinetic equations to describe. Rule-based models allow interactions to be expressed between binding domains on molecules, and rule-based simulators build complexes during the simulation. This obviates the need to provide equations for all possible complexes. Rule-based simulators are also stochastic and thus can deal with the small copy numbers of proteins and complexes in the PSD.

To construct models of synaptic plasticity with realistic numbers of proteins, we have combined the rule-based Kappa simulator with the NEURON simulator of compartmental models of the electrical activity of neurons to give the KappaNEURON hybrid simulator (Sterratt *et al.* 2014). We evaluate KappaNEURON by using it to implement existing models of bidirectional synaptic plasticity, assessing how conveniently the models are expressed, the effect of stochastic simulation and the importance of modelling electrical and molecular aspects simultaneously.

Sterratt, DC, Sorokina, O & Armstrong, JD (2014). Integration of rule-based models and compartmental models of neurons. Accepted in the Proceedings of the Third International Workshop on Hybrid Systems Biology, Vienna, 2014. http://arxiv.org/abs/1411.4980
Zeng S & Holmes, WR (2010) J Neurophysiol 103:1798
Zhabotinsky, AM & al. (2006) J Neurosci 26:7337

Poster Ref: P3-A-013
Theme: A: Development

Lifespan trajectories of the human white matter microstructure: preliminary results from the human connectome project.

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Background: Understanding the normal progression of brain WM microstructure across the lifespan can deepen our understanding of how WM 'integrity' modulates healthy cognitive functioning. Previous WM studies testing specific theories linking development and ageing processes in humans – *e.g.*, "last-in-first-out", "anterior-to-posterior gradient" or "gain-predicts-loss" – have led to conflicting results (Westlye *et al.*, 2010, Yeatman *et al.*, 2014). We thus aim to characterise the lifespan trajectories of WM microstructure using the exceptionally high-quality diffusion imaging dataset from the Human Connectome LifeSpan Pilot Project (http://lifespan.humanconnectome.org/).

Methods: *Participants' age-groups: 8-9, 14-15, 25-35, 45-55, 65-75 (ntot=26).
* Diffusion imaging: 1.5mm isotropic, MB 3, 75 directions, RL and LR phase-encoding polarities; b= 1000 and 2500.
All analyses were carried out in FSL:
- Tract-Based Spatial Statistics (TBSS), with an optimised registration protocol to account for the wide age range of the participants.
- Probabilistic tractography: bedpostX (3 fibres), probtrackX and AutoPtx (de Groot *et al.*, 2013).

Results: * Average fractional anisotropy (FA) and mean diffusivity (MD) projected onto the whole TBSS skeleton showed a non-linear age dependence, following an inverted U-pattern for FA, and a U-pattern for MD. The model qualitatively describing best the trajectories in the skeleton was a rational polynomial fit (cubic numerator, linear denominator).
* In each tract virtually reconstructed using probabilistic tractography, the same qualitative fits modelled well the average FA and MD lifespan trajectories. These (inverted) U curves showed varying peaks for each tract across the lifespan, with the anterior thalamic radiation and the cingulum peaking the latest for FA (Figure 1).

Conclusion and Perspective: We found qualitatively similar (inverted) U shaped trajectories to previous lifespan WM studies (*e.g.*, Westlye *et al.*, 2010; Lebel *et al.*, 2012). Based on our preliminary data, there was no clear support for any of the developmental-ageing theories based on the diffusion information in each tract. Future analyses will exclude regions of crossing fibres (confounding effects on FA and MD), and include more participants in each age range.

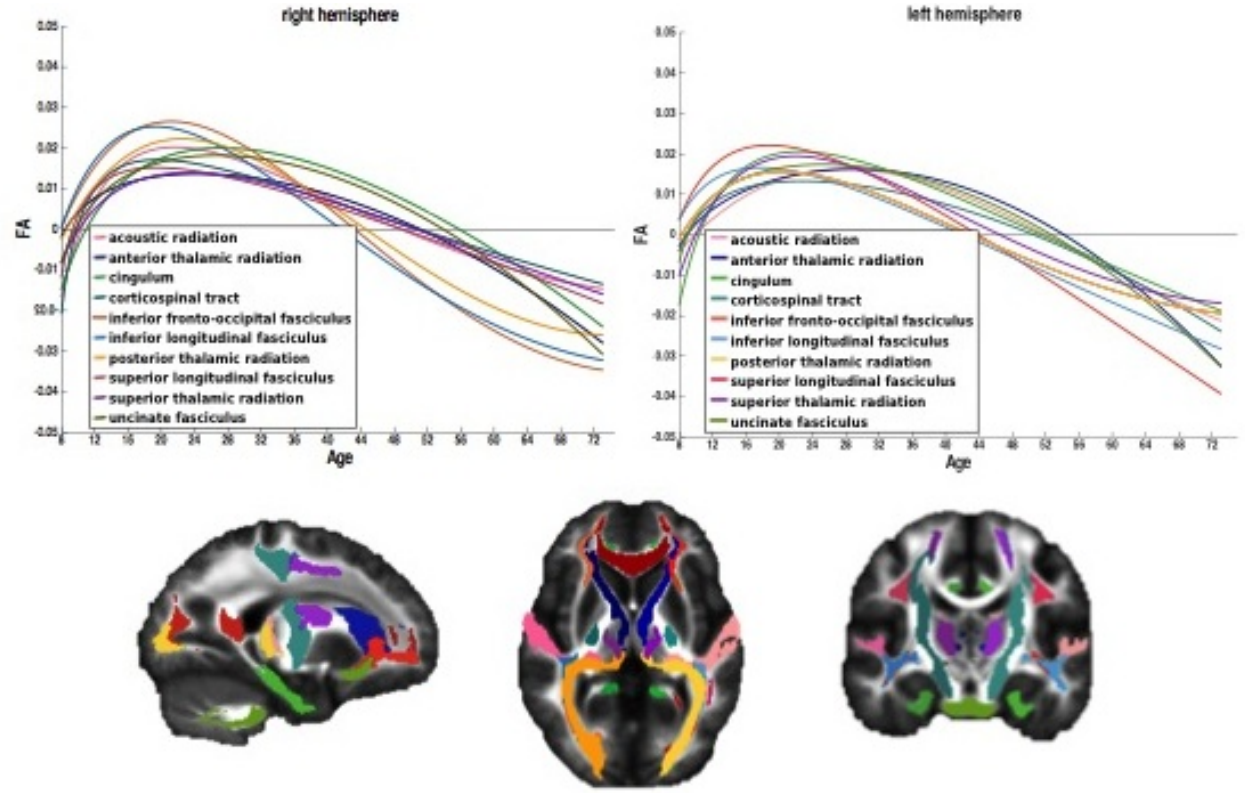

Figure 1: Normalised, averaged FA values in each left and right major tract obtained with probabilistic tractography (probtrackX) and an automatic script (AutoPtX) in FSL.

Poster Ref: P3-A-014

Theme: A: Development

Maternal ghrelin elicits transgenerational changes in emotional processing and stress responsiveness.

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Stress during pregnancy can have a profound impact on the emotional state of both the mother and offspring. A tremendous amount of work has focused on stress hormones of the hypothalamic-pituitary-adrenal (HPA) stress axis as the primary cause of such changes. However, the Goosens lab has recently identified a critical role for ghrelin and growth hormone in affective dysregulation following chronic stress, acting independently of the HPA axis. Because hunger, a stress state that elevates ghrelin in humans, has been closely linked to transgenerational changes in stress responsivity and health, we hypothesize that elevated maternal ghrelin signalling during pregnancy may give rise to depressive behaviours in the mother, and also alter aversive processing and stress responsiveness in the offspring.

Rat dams were exposed to an agonist of the ghrelin receptor (growth hormone secretagogue receptor, or GHSR), during pregnancy, mimicking the prolonged enhancement of ghrelin that is observed in chronically stressed animals. We observed deficits in behaviours related to depression and risk-taking in dams following weaning such as the absence of sucrose preference, and increased exploration of the open arms of an elevated plus maze, compared to controls. Dams exposed to MK0677 also had elevated circulating ghrelin that persisted for a month postpartum. The adult offspring of MK0677-treated dams displayed diminished fear memory recall following auditory Pavlovian fear conditioning, and this was found to be related to circulating ghrelin, but not corticosterone.

These data indicate a role for circulating ghrelin in the emotional state of both mothers and their offspring. Ghrelin-growth hormone signalling in the brain is a potential developmental risk factor for emotional processing disorders, and provides a potential therapeutic target that may improve the quality of life of people that suffer with poor stress coping.

Poster Ref: P3-A-015
Theme: A: Development

Secretions from the placenta alter neuronal development in hypoxia.

Thomas Phillips and Patrick Case
University of Bristol

Psychological disorders such as autism, schizophrenia and ADD are thought to originate partially due to insults to the foetus during pregnancy. Events like infection or hypoxia reoxygenation during pregnancy have been shown to increase the risk of psychological disorders in later life. While the placenta normally acts as a protective barrier between the mother and the foetus we have found during a hypoxic insult it releases damaging molecules into the foetal circulation.

We modelled obstetric complication and exposed a placental trophoblast barrier to variable oxygen levels. We collected tissue culture media from below the barrier and analysed its contents. We found that the placental barrier secreted increased levels of glutamate when exposed to hypoxia and hypoxia reoxyegenation.

When E18 cerebral cortical neurons and hippocampal slices were exposed to this media we found a reduction in the number and change in the composition of NMDA and GABA receptors. We also found a reduction of dendrite length and an increase in astrocyte number.

To examine this *in vivo* we exposed the conditioned media into the brain of P4 rats and then collected the brains at P30. We discovered the conditioned media from hypoxia exposed trophoblast barriers results in a reduction in Parvalbumin positive neurons and an increase in tyrosine hydroxylase positive cells at the thalamus, cortex and hippocampus. We also found increases in GFAP staining, reduction of dendrite length and number and a general cell number decrease.

Our hypothesis is that factors including glutamate, released from the placenta during hypoxia might enter the foetal circulation and cause changes in the developing brain. These changes are similar to the types of changes seen in post mortem brains of patients with Schizophrenia.

We have attempted to negate these changes either by treating the mother's placenta with a drug delivery antioxidant nanoparticle to prevent the changes in the placenta secretions. This treatment has proven to be successful in preventing the changes in dendrite length *in vitro* and we are currently performing a *in vivo* experiment in collaboration with the University of Alberta.

Poster Ref: P3-A-016

Theme: A: Development

Self-organization of information processing in developing neuronal networks.

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Human brains possess extraordinarily sophisticated information processing capabilities, which rely on the coordinated interplay of several billions of neurons. Despite recent advances in characterizing functional brain circuitry, however, it remains a major challenge to systematically understand the principles of how functional neural networks develop and maintain these processing capabilities. Using multi-electrode recordings in mouse hippocampal and cortical neurons over the first 4 weeks *in vitro*, we demonstrate that developing neuronal networks increase their information processing capacities, as quantified by transfer entropy and active information storage [1], [2]. The increase in processing capacity is tightly linked to a self-organization of the collective neural dynamics to a critical state [3] ($r=0.68$, $p<1e-9$; $r=0.55$, $p<1e-6$ for transfer and storage, receptively). The increase of processing capacity with approaching a critical state has been predicted by modelling studies [4], and our results are the first to confirm this prediction experimentally. We further demonstrate that emerging information processing capacities are paralleled by the development of a topology that supports efficient neuronal communication across the functional network. In summary, our results suggest that neural networks self-organize to a critical state during maturation resulting in increased processing capabilities and representational capacity, by shaping both their dynamics and their topology.

References

[1] J. T. Lizier, M. Prokopenko, and A. Y. Zomaya, “Local information transfer as a spatiotemporal filter for complex systems,” Phys. Rev. E, vol. 77, no. 2, p. 026110, Feb. 2008.

[2] T. Schreiber, “Measuring Information Transfer,” Phys. Rev. Lett., vol. 85, no. 2, pp. 461–464, Jul. 2000.

[3] H. E. Stanley, “Introduction to Phase Transitions and Critical Phenomena,” Introd. Phase Transit. Crit. Phenom. H Eugene Stanley Pp 336 Foreword H Eugene Stanley Oxf. Univ. Press Jul 1987 ISBN-10 0195053168 ISBN-13 9780195053166, vol. -1, Jul. 1987.

[4] J. Boedecker, O. Obst, J. T. Lizier, N. M. Mayer, and M. Asada, “Information processing in echo state networks at the edge of chaos,” Theory Biosci., vol. 131, no. 3, pp. 205–213, Sep. 2012.

Poster Ref: P3-A-017

Theme: A: Development

Assessing language lateralisation in preschoolers using functional transcranial Doppler sonography.

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The developmental trajectory of the typical pattern of left hemisphere dominance for language has received renewed attention in recent years (Toga & Thomspon, 2003; Bishop, 2013). However, research focusing on language dominance in children has been hampered by the strict movement constraints of many neuroimaging techniques. Consequently, many studies of child language take place with neonates using passive speech perception tasks (Dehaene-Lambertz *et al.*, 2010; Mingawa-Kawai *et al.*, 2012). Those studies using higher order language tasks requiring comprehension and production of language most often take place after children have begun school (Szaflarski *et al.*, Groen et al 2012). These studies report left-lateralised activity which develops with age (Szaflarski *et al.*, 2012) and proficiency (Groen *et al.*, 2012). However, given that the acquisition of literacy is thought to affect the neurobiology of oral language processing (Dehaene *et al.*, 2010) a question which remains is whether early leftward asymmetries relate to proficiency before the onset of literacy.

Functional transcranial Doppler sonography (fTCD) is a fast and non-invasive way of establishing hemispheric dominance during cognitive tasks (Deppe *et al.*, 2004). The technique measures event related changes in blood flow velocities in left and right middle cerebral arteries and shows concordance with other methods of measuring functional lateralisation, such as the Wada test (Knecht *et al.*, 2001) and fMRI (Somers *et al.*, 2011).

In the current study we used fTCD to examine lateralisation of language processing in 17 preschool children (Mean age = 3.5 years (range 3.2 – 4.1)). Children completed an fTCD animation description task (Bishop *et al.*, 2013) and a battery of standardized and experimental language assessments. As a group the children showed left lateralisation (Laterality Index mean = 1.83 (sd 3.7) which approached significance (i.e. when contrasted with zero) ($t(16) = 2.03$, $p = .059$). Eleven of the children were significantly left lateralised, one was significantly right lateralised, and 5 showed low lateralisation. Concurrent correlations between the strength of lateralised responses and offline behavioural language measures were not found.

The same children were tested again 12months later on the same fTCD measure and also a behavioural test battery. The longitudinal relationship between hemispheric lateralisation and behaviour will be reported. These data have the potential to offer unique insights into individual variability of functional lateralisation and its relationship to language and literacy development in the early years.

Poster Ref: P3-A-018

Theme: A: Development

Dopamine and memory dedifferentiation in aging.

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The dedifferentiation theory of aging proposes that a reduction in the specificity of neural representations causes declines in complex cognition as people get older, and may reflect a reduction in dopaminergic signaling. The present pharmacological fMRI study investigated episodic memory-related dedifferentiation in young and older adults, and its relation to dopaminergic function, using a randomized placebo-controlled double-blind crossover design with the agonist Bromocriptine (5mg) and the antagonist Sulpiride (400mg). We used multi-voxel pattern analysis to measure memory specificity: the degree to which distributed patterns of activity distinguishing two different task contexts during an encoding phase are reinstated during memory retrieval. As predicted, memory specificity was reduced in older adults in prefrontal cortex and in hippocampus, consistent with an impact of neural dedifferentiation on episodic memory representations. There was also a linear age-dependent dopaminergic modulation of memory specificity in hippocampus reflecting a relative boost to memory specificity on Bromocriptine in older adults with poorer memory. This differed from generalized effects of both agents on task specificity in the encoding phase. The results demonstrate a link between ageing, dopaminergic function and dedifferentiation in the hippocampus.

Poster Ref: P3-A-019

Theme: A: Development

Influence of colour and luminance on visual working memory - a study using EEG.

Maciej Kosilo[1], Jasna Martinovic[2] and Corinna Haenschel[1]

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Early encoding processes in working memory (WM) have been shown to have significant impact on performance (Haenschel *et al.*, 2007). Although current reports point to the interplay between perception and WM (Pasternak & Greenle, 2005), the role of perceptual factors in WM is not clear. Separate visual channels process chromatic and achromatic (luminance) information. In line with accounts of everyday vision benefitting from fast luminance projections transmitted through magnocellular pathway (Bar, 2003), we expected that luminance will benefit performance on WM task more than chromatic information. In a delayed discrimination task participants had to remember up to 3 abstract shapes. The stimuli were defined along different directions in cardinal colour space (Derrington *et al.*, 1984), creating luminance-defined stimuli, two classes of chromatic-only stimuli, and a mixed-signals stimuli. The stimuli were equated in terms of salience through an initial psychophysical same/different threshold task. Luminance-defined shapes led to higher accuracy and faster reaction times. Event-related potentials time locked to the last item in encoding array revealed that early visual component P1 was characterised by a greater amplitude in response to luminance stimuli. Component N1 peaked at parietal and frontal sites earlier for luminance-defined stimuli, reflecting the luminance speed advantage. The results point to the differential contribution of different cone signals to WM performance, highlighting the importance of early encoding in these tasks. In line with previous studies (Kveraga *et al.*, 2007) we hypothesise that fast luminance projections may serve as an early trigger for top-down processing, affecting the efficiency of WM encoding.

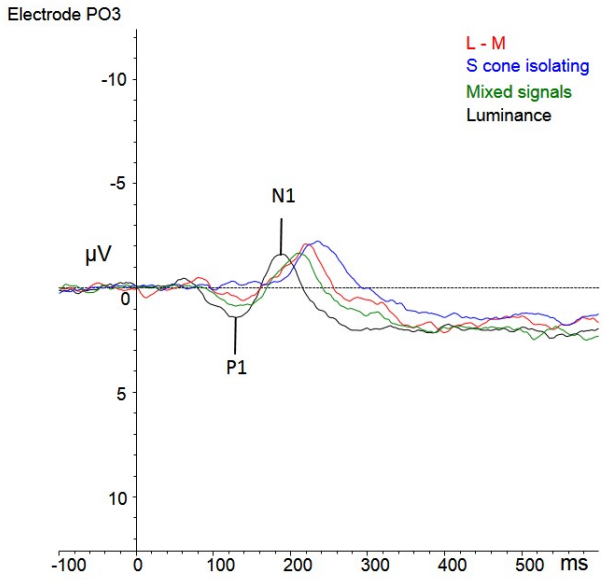

Figure 1: Event-related potentials measured at electrode PO3 during encoding abstract shapes into working memory. Shapes were defined along different directions in Derrington-Krauskopf-Lennie colour space (DKL), allowing for differentia stimulation of different postreceptoral mechanisms.

Waveform in response to achromatic, luminance-defined stimuli is shown as a black line, chromatic isoluminant L-M is red, S cone isolating is blue and mixed signals (which contained both chromatic and luminance information) is shown in green.

Luminance-defined stimuli elicited greater early visual component P1 and earlier N1 component than other conditions, demonstrating processing speed advantage.

Poster Ref: P3-A-020

Theme: A: Development

Functional characterization of the dyslexia candidate gene KIAA0319.

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Dyslexia is a disorder characterized by difficulties in reading regardless of good educational environment and normal intellectual capacities. The biological basis of dyslexia is not understood but it has a strong genetic component, with an estimated heritability around 70%, and it is likely to be caused by the combination of genetic and environmental factors. Several genes have been identified as dyslexia candidates from which DCDC2, DYX1C1 and KIAA0319 count with the strongest supporting evidence. DYX1C1 localizes at the basal body, the centriole at the base of the cilia, and DCDC2 on its microtubules. Both proteins play a role in regulating cilia length [1,2]. Cilia are sensory organelles that have shown to be very important for many processes, including neural signalling [3] axonal guidance [4] and cortical development [5]. During CNS development and also in the adult brain motile cilia cause a flow of cerebrospinal fluid that guide neuronal migration [6].

Our work focus on the functional characterization of KIAA0319. Knockdown in rats impairs neuronal radial migration during cortex development [7] , a phenotype that has also been observed in DCDC2 and DYX1C1 knockdowns. KIAA0319 encodes a transmembrane protein with five PKD domains in its structure, a feature that was first identified in polycystic kidney disease proteins that play an important role in cilia function. It has also been observed that KIAA0319 is upregulated in ciliated tissue [8]. These observations and our preliminary results support our hypothesis of a role of KIAA0319 in cilia biology, and together with the evidence from other candidate genes points to a link between this organelle and dyslexia.

Bibliography

1. Chandrasekar, G. *et al.*, PLoS One 8, e63123 (2013).
2. Massinen, S. *et al.* PLoS One 6, e20580 (2011).
3. Louvi, A. & Grove, E. Neuron 69, 1046–60 (2011).
4. Lee, J. H. & Gleeson, J. G. Neurobiol. Dis. 38, 167–72 (2010).
5. Métin, C. & Pedraza, M. Neuroscientist (2014).
6. Sawamoto, K. *et al.* Science 311, 629–32 (2006).
7. Paracchini, S. *et al.* Hum. Mol. Genet. 15, 1659–66 (2006).
8. Ivliev, A. E. *et al.* PLoS One 7, e35618 (2012).

Poster Ref: P3-A-021

Theme: A: Development

Environmental enrichment accelerates the maturation of murine striatal inhibitory circuitry and impacts juvenile striatally-mediated behaviours.

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Introduction: Environmental enrichment (EE) provides extra sensory, motor and social stimuli. EE accelerates striatal perineuronal net (PNN) maturation and accelerates the onset of striatally-mediated behaviours. Striatal PNNs are associated with Parvalbumin (PV) inhibitory interneurons, regulators of activity within this nucleus. Mature PV neurons within the adult striatum depend upon the presence of Brain-Derived Neurotrophic Factor (BDNF) protein. We investigated the impact of EE upon PV and BDNF maturation within the striatum; the impact of lifelong EE upon the association of striatal PNNs and PV neurons; and assessed the effect of EE upon juvenile striatally-mediated behaviours.

Methods: Animals were raised in enriched or standard housing. PNNs and PV neurons were assessed using immunohistochemistry, and BDNF levels using an ELISA. Juvenile ultrasonic vocalisations (USV) were recorded and number, duration and type of calls analysed. Data were analysed using univariate ANOVA and repeated measures ANOVA.

Results: Enriched pups demonstrated higher density of PV neurons (P10, p=0.001; P15, p=0.005, n=4-6) and higher levels of BDNF protein (P10, p=0.009, n=8) within the striatum. Analysis of USV call number, duration and types between P7 and P15 revealed that enriched pups (n=22) show a differing call profile when compared to standard pups (n=26). Enriched adults (n=3) had a significantly higher density of PV neurons present within the striatum (P=0.016) than did standard animals (n=3), and a greater level of overlap between PV neurons and PNNs (P=0.001) despite EE having no effect upon the number of striatal PNNs (P=0.236).

Conclusions: EE accelerated the maturation of PV inhibitory interneurons and BDNF within the striatum. Around the same age, EE impacted USV call production, known to be a striatally-mediated behaviour. Life-long EE appears to increase the level of PV expression within the adult striatum with no effect upon PNN expression. Thus, exposure to EE influenced the anatomical, molecular and functional development of the striatum, and continued to impact striatal anatomy into adulthood.

Theme B: Molecular, Cellular and Synaptic Mechanisms

Posters P3-B-001 to P3-B-043

Poster Ref: P3-B-001

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Regulation of TREM expression in microglia.

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Mechanisms preventing inappropriate or excessive activation of microglia are important to limit the risk of CNS inflammatory dysregulation and neurodegeneration. The TREM family of receptors regulate the strength of immune responses in myeloid cells, including microglia, through signals transduced by amplifying (TREM1) and inhibitory (TREM2) receptors. Factors which affect the expression of TREM receptors and ligands may be important influences on immunoregulation in the brain. We sought to determine how expression of the TREM system is regulated by microglial polarisation *in vitro* and CNS inflammation *in vivo*.

Purified adult mouse microglia or the BV2 microglial cell line were polarised with LPS or IL-4. LPS exerted opposing effects on TREM1 and TREM2 expression. TREM1 mRNA was induced whereas TREM2 mRNA and protein expression were suppressed by LPS. In contrast, IL-4 had negligible effects on both receptors. LPS-mediated suppression of TREM2 and induction of TREM1 were reversed by inhibition IκB kinase inhibition suggesting NF-κB as a key and opposing regulator of activating and inhibitory TREMs in microglia. We established that microglia express endogenous ligands for TREM2 indicating the potential for autocrine signalling, however ligand expression was not affected by microglial polarisation. The suppressive effects of LPS on TREM2 expression were not limited to TLR4 stimulation as ligands for TLR1/2, TLR3 and TLR9 had similar actions, but effects on TREM1 were TLR subtype-dependent. We also found induction of TREM1 and suppression of TREM2 expression *in vivo* at early time-points after acute LPS-induced intracerebral inflammation.

These data reveal NF-κB-dependent regulation of activating and inhibitory TREM receptors in microglia and indicate changes in the balance of TREM expression favouring amplification of neurotoxic innate immune responses during the initial phase of CNS inflammation.

Poster Ref: P3-B-002

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Increased Amyloid-β binding alcohol dehydrogenase (ABAD) activity causes alterations in the lipid and fatty acid composition of cells.

Zoe Allen, Terry Smith and Frank Gunn Moore

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Introduction: Changes in glucose metabolism have been observed in the brains of Alzheimer's disease sufferers. This suggests that neurons require an alternative energy source that can bypass glycolysis in order to produce energy. The oxidation of fatty acids is crucial at this point as the products of this catabolism can feed into the second stage of the respiratory cycle. ABAD is a key enzyme in the production of ketone bodies *via* fatty acid oxidation and in the brain has been found to be upregulated in AD [1, 2]. Additionally, ABAD is upregulated under conditions of energy deprivation and increased ketogenesis further highlighting a role for ABAD in metabolism [3, 4]. Previous research has found that membrane fluidity affects Aβ production *via* changes in Amyloid Precursor Protein (APP) cleavage [5]. Consequently, fluctuations in fatty acid and lipid composition of cells could be affecting Aβ production. Within this study, we show that glucose concentration caused an increase in ABAD activity and that this activation of ABAD subsequently affects the metabolism of fatty acids and lipids.

Methods: ABAD activity assay was conducted using the fluorogenic probe (-)-CHANA, which when oxidized by ABAD produces the fluorescent product CHANK. ESI-MS & GC-MS were used to determine if ABAD affects fatty acid and lipid composition in cells.

Results: ABAD activity was found to increase when glucose levels were decreased. Further effects downstream in lipid and fatty acid metabolism have also been observed upon changes in glucose levels and ABAD expression.

Conclusion: Increased ABAD activity suggests that cells are relying on the production of ketone bodies as an alternative energy source. Downstream effects of modified ABAD activity include changes in lipid and fatty acid content suggesting that the β-oxidation of fatty acids is altered.

1. He, X.Y., *et al.*,. Journal of Biological Chemistry, 1999. 274(21): p. 15014-15019.
2. Lustbader, J.W., *et al.* Science, 2004. 304(5669): p. 448-52.
3. Du Yan, S., *et al.* The Journal of biological chemistry, 2000. 275(35): p. 27100-9.
4. Yao, J., *et al.* PloS one, 2011. 6(7).
5. Kojro, E., *et al.* Proc Natl Acad Sci U S A, 2001. 98(10): p. 5815-20.

Poster Ref: P3-B-003

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Identifying potential peripherally accessible biomarkers in Batten disease.

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Batten disease or Neuronal ceroid lipofuscinosis (NCL) is the most frequent autosomal- recessive neurodegenerative disease of childhood [1]. There are 13 forms of NCL caused by mutations in different genes affecting lysosomal function. All of them lead to the same features of clinical progression including, the accumulation of autofluorescent storage material in the lysosome (the main hallmark of these conditions), early synaptic loss and premature death [2, 3]. The most prevalent forms of this devastating condition are the CLN1 disease variant or infantile NCL (INCL) and the slightly later onset CLN3 disease or Juvenile NCL (JNCL) variant [4, 5]. Here we have used a proteomic based approach in murine models of NCL disease to demonstrate that although the gross appearance of CLN3 KO muscle fibres remains unchanged at early disease stages, there are significant molecular perturbations detectable at early time points. These include but are not limited to pathways involved in small molecule biochemistry and mitochondrial dysfunction. Thalamic synapses are an early pathological target in NCL [6, 7, 8]. We hypothesise that a tractable biomarker will be something which is constitutively expressed, but which changes in response to a mutation of interest in a tissue specific manner. We therefore compared the changes observed in muscle and thalamic synaptic proteomes. Constitutively expressed proteins were examined for higher order functional clustering and candidates were temporally tracked using label free proteomic profiling of CLN1 KO muscle throughout the time course of CLN1 disease progression. Here we identify multiple potential peripherally accessible biomarkers of disease progression which are mitochondrial in origin and whose expression is conserved in both CLN1 and CLN3 forms of NCL disease.

References: 1. PMID: 8576551, 2. PMID: 12644737, 3. PMID: 15965709, 4. PMID: 7553855, 5. PMID: 12125808, 6. PMID: 19640925, 7. PMID: 16242638, 8. PMID: 18091563

Poster Ref: P3-B-004

Theme: B: Molecular, Cellular and Synaptic Mechanisms

In vitro electrophysiological characterisation of neuronal diversity in the nucleus reuniens of adult mice.

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The nucleus reuniens (Re) is a ventral nucleus of the midline thalamus. Recently, interest in Re has grown following neuroanatomical, electrophysiological and behavioural studies which suggest it plays a substantial role in cognitive processes. Furthermore, dysfunction of Re may contribute to specific dementias in man. This study seeks to provide an *in vitro* characterisation of the electrophysiological properties of individual Re neurons, using whole-cell current clamp techniques. Using a Kgluconate-based pipette solution 144 neurons were recorded from 300 µm coronal slices taken from 16-18 week old C57/Bl6 mice. Neurons were initially classified as either bursty (69/144) or non-bursty (75/144) based on their ability to fire two spikes with an instantaneous frequency of >100 Hz in response to a depolarising current step from a prestimulus potential of -80 mV. Non-bursty neurons were subsequently divided into 3 groups (accommodating (n=57), accelerating (n=11) or regularly spiking (n=6)) based on the slope of a linear fit of the first 10 instantaneous frequencies in response to a 60 pA current injection from -80 mV. A range of intrinsic membrane properties were assessed across these populations. Differences between groups were observed in resting membrane potential ($p=0.006$), firing frequency at rest ($p=0.001$), firing frequency in response to a series of current injections ($p<0.001$), rheobase ($p=0.025$) and ADP amplitude following a single spike ($p<0.001$), further suggesting a distinct heterogeneity in the neurophysiological properties of Re neurons. A series of current clamp recordings at a more depolarised prestimulus potential (-72 mV) made in a subset of bursty and accommodating neurons, showed that differences between these populations in firing patterns and ADP were attenuated at this potential. Pharmacological interventions suggest a key role for T-Type Ca^{2+} channels in bursting cells. In conclusion, we observed 4 functionally distinct populations of neurons within the Re. These data represent an important step forward in our understanding how neurons in the Re may behave in the context of cognitively-relevant neuronal networks.

Poster Ref: P3-B-005
Theme: B: Molecular, Cellular and Synaptic Mechanisms

Functional presynaptic kainate receptors in layer II and V of the rat entorhinal cortex.

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University of Bath

We have been studying the role of kainate receptors (KARs) in the entorhinal cortex (EC) and have recently (1) shown multiple roles for different KAr subtypes in synaptic transmission and synchronisation of neuronal networks in layer III (L3). In the current experiments, we have begun to extend these studies to other layers of the EC. Whole cell patch-clamp was used to record spontaneous excitatory postsynaptic currents (sEPSCs) in principal neurones in layers II (L2) and layer V (L5) in slices from Wistar rats (P28-38). sEPSCs were used as a reporter of presynaptic glutamate release.

Baseline sEPSCs in the two layers showed clear differences. Mean (±sem) interevent interval (IEI, inversely proportional to frequency) in L2 was 0.31±0.02s, considerably less than in L5 (1.16±0.06s). Average amplitude (15.3±0.4pA v 10.0±0.2pA) was greater in L5 showing fundamentally differences in glutamate release in the two layers.

The non-specific KAR agonist, kainic acid (KA; 400 nM), decreased IEI in L5 during the first 5 minutes of application from 2.2±0.2s to 1.2± 0.1s ($P<0.001$, n=4; Kolmogorov-Smirnov (KS) test), reflecting a substantial increase in frequency, although the amplitude of sEPSCs was unchanged. This indicates that presynaptic KAR can facilitate glutamate release in L5. However, IEI of sEPSCs returned to control levels after 15 min even in the presence of KA, suggesting that presynaptic KARs may slowly desensitise, or that the increase in release depletes releasable stores. In contrast to KA, specific activation of GluK1-containing KARs with the selective agonist, ATPA, increased IEI in L5 from 1.2±0.1s to 1.6±0.1s, reflecting a 25-30% decrease in frequency ($P<0.005$, n=7; K-S test). ATPA also increased IEI In L2 from 0.31±0.02s to 0.44±0.01s ($P<0.001$, n=3; KS). Amplitude was unchanged in either layer.

Thus, non-specific activation increased glutamate release in L5, but activation of GluK1-containing KARs decreased release in both layers. These studies show substantial differences between L2/L5 compared to L3 where ATPA increased release [1]. Further studies will delineate the integrated role of KAR in normal and pathologically oscillating neuronal networks.

1. Chamberlain *et al.*, (2010) Hippocampus 22:555-76

Poster Ref: P3-B-006

Theme: B: Molecular, Cellular and Synaptic Mechanisms

The role of CaMKII-alpha in experience dependent structural plasticity of Layer2/3 pyramidal dendritic spines in mouse barrel cortex.

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Most functional plasticity studies to date have focused on Layer2/3 neurons, while structural plasticity remains largely uncharacterized in these layers. It is not clear from the literature on visual and somatosensory cortex whether L2/3 neurons show significant levels of structural plasticity in response to sensory deprivation, whilst it is clear that they show substantial functional plasticity that is CaMKII dependent (Glazewski *et al.* (2000). To address this issue we investigate experience dependent structural plasticity of the basal dendritic spines L2/3 pyramidal neurons in the barrel cortex. C57Bl6-Jax mice were injected intracranially with AAV-Cre(CaMKII)-GFP and AAV-Flex-GFP, to target expression of GFP (under the control of the CaMKII-alpha promoter) in a sparse population of L 2/3 pyramidal neurons. Using 2-photon microscopy, chronically intracranial windowed GFP mice were then imaged to quantify basal turnover. Mice were then subjected to sensory (chessboard whisker CWD) deprivation and the imaging paradigm timed so that spines were quantified and characterised 24 hours post deprivation, with subsequent 3 day imaging time points extending up to two weeks post CWD. This allowed for the identification of New Persistent Spines. To investigate the role of CaMKII-alpha in the structural component of experience-dependent plasticity in the barrel cortex, we imaged double virus injected CaMKII-Threonine-286-Alanine (CaMKII-T286A) mutant mice, and characterised spine density, morphology, turnover and persistence before and after CWD. Preliminary results show that CaMKII-T286A mice have a delayed response in spine dynamics to CWD, compared to that of WT controls. The degree of structural plasticity in CaMKII-T286A mice was also decreased, with a smaller percentage difference in spine dynamics at 1 and 4 days post CWD, compared to WT controls. Morphology analysis will reveal if these changes are specific to distinct classes of dendritic spines. These data, for the first time, suggest a role for CaMKII-alpha in the initial phases of structural changes in basal dendritic spines of L2/3 neurons, and therefore support the hypothesis that structural plasticity underlies the functional experience-dependent plasticity observed in the mouse barrel cortex.

Poster Ref: P3-B-007

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Mitochondria and synaptic stability.

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Mitochondria are the 'power-houses' of all cells, generating ATP to fuel numerous pathways which are vital for cellular form and function [1]. Neuronal processes and synapses present a constant demand for ATP to maintain ionic gradients and neurotransmission events [2], promoting sub-populations of mitochondria to be enriched pre- and post-synaptically [3, 4]. These mitochondria display unique enzymatic [5], calcium buffering [6, 7] and antioxidant properties [8] and have thus been associated in the pathogenesis of a variety of neurodegenerative diseases where the synapse is the primary target. We have characterised the proteomes of these synaptic and non-synaptic mitochondria at a basal level by following early biochemical isolation methods [5] and adopting a label-free proteomic approach, generating a species-specific molecular fingerprint. Our study has demonstrated distinct proteomic profiles between the two sub-populations of mitochondria, dependent upon sub-cellular localisation. Quantitative fluorescent western blotting was used to validate the proteomic studies in a range of species, suggesting that the data may be an accurate reflection of the fingerprint for distinct mitochondrial populations. These results also suggest that mitochondrial neuronal sub-populations and their relative protein abundances are likely conserved between mammalian species. Following this, *in vivo* assays of mitochondrial candidates using *Drosophila* larval fillet preparations were performed. Our data demonstrate that selective knock-down of intrinsic mitochondrial proteins alter synaptic morphology which may contribute to pathological processes during ageing and neurodegenerative disease.

Poster Ref: P3-B-008

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Willin/FRMD6 involvement in signalling: biochemistry and proteomics.

Andrew Tilston-Lunel and Frank Gunn-Moore

University of St Andrews

Background: FRMD6/Willin was first identified as a binding partner of Neurofascin in a yeast two-hybrid screen of a rat sciatic nerve library [1]. Our laboratory has demonstrated that Willin is an upstream component of the Hippo pathway, a growth controlling pathway in epithelial cell and in rat sciatic nerve fibroblasts [2, 3].

Method: We created SHSY-5Y cell lines that either overexpressed Willin or knocked down Willin by the use of a specific shRNA. We have performed a triple SILAC experiment to study the total proteome changes and phosphoproteome changes.

Results: The loss of Willin caused a phenotypic response whereby the SHSY5Y cells showed enhanced neurite outgrowth without the treatment of retinoic acid. This neurite outgrowth has been due to the activation of ERK1/2. We have obtained quantitative data for the SILAC and phosphoSILAC proteomes.

Conclusion: Preliminary biochemical data suggests that Willin might act as a suppressor of the MAPK pathway. We have validated a few of the hits from the SILAC screens and we will be investigating these hits further for their physiological relevance and functions.

1. Gunn-Moore, F.J., *et al.*, A novel 4.1 ezrin radixin moesin (FERM)-containing protein, 'Willin'. FEBS Lett, 2005. 579(22): p. 5089-94.
2. Angus, L., *et al.*, Willin/FRMD6 expression activates the Hippo signaling pathway kinases in mammals and antagonizes oncogenic YAP. Oncogene, 2012. 31(2): p. 238-50.
3. Moleirinho, S., *et al.*, Willin, an upstream component of the hippo signaling pathway, orchestrates mammalian peripheral nerve fibroblasts. PLoS One, 2013. 8(4): p. e60028.

Poster Ref: P3-B-009

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Defective axonal mitochondrial trafficking in a neuronal model of major mental illness.

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Disrupted In Schizophrenia 1 (DISC1) was first identified as a candidate gene for major mental illness due to its disruption by a balanced t(1;11) translocation that co-segregates with psychiatric illness in a large Scottish family. DISC1 regulates the trafficking of mitochondria in axons and this potentially implicates mitochondrial homeostasis in psychiatric illness. We have access to a novel mouse model of the t(1:11) translocation developed by Sanofi-Aventis. Compared to wild type mice, heterozygous t(1;11) mice exhibit reduced DISC1 mRNA and protein expression, consistent with the reduced DISC1 expression levels in lymphoblastoid cell lines derived from translocation carriers in the Scottish family. To test for potential effects of the t(1:11) translocation on axonal mitochondrial trafficking, hippocampal neurons isolated from homozygous and wild type mouse embryos were used for time-lapse imaging of mitochondrial motility.

Measurements were collected from fifty axon segments over three independent cultures of neurons from each genotype. Several parameters were analysed, including percentage motility, direction of movement, and displacement. No change in the number of moving mitochondria, or their direction of movement was detected. However, net displacement of retrograde, but not anterograde, moving mitochondria was significantly lower in homozygous versus wild type neurons, lending additional support to our hypothesis that mitochondrial trafficking defects increase susceptibility to psychiatric illness. Future work will include repeating this work in heterozygous mice which are a more biologically relevant model of the human translocation carriers, and determining the mechanism by which the translocation causes this specific effect upon directional mitochondrial displacement.

Poster Ref: P3-B-010

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Characterising proteinase-activated receptor 2 (PAR2) using novel small molecules.

Serge Moudio

Strathclyde University

G-protein coupled receptors (GPCRs) are the richest source of targets for the pharmaceutical industry. Proteinase-activated receptor 2 (PAR2), a subtype of GPCRs, has recently received increasing interest due to their potential neuroprotective role in CNS diseases. Investigating the role and properties of PAR2 in CNS was previously made difficult by the limited selectivity and potency of PAR2 activators. Recently however, novel small molecule PAR2 activators with high potency and good stability have been developed allowing further investigation.

PAR2 activation has previously been shown to increase intracellular Ca^{2+} levels in both neurons and astrocytes. In the present study, we have utilised the recently developed PAR2 activators, GB110 and AC264613 and the proposed PAR2 antagonist, GB88 to determine their effects on intracellular Ca^{2+} levels in rat primary hippocampal cultures (12-15 DIV). In agreement with previous studies, our results demonstrate that PAR2 activation results in an increase of calcium concentration in both neurons and astrocytes with GB110 and AC264613 resulting in an increase of 3.72 ± 12 % (n=15, $P<0.05$) and 2.1 ± 7 % (n=21, $P<0.05$) respectively in neurons and 2.23 ± 9 % (n=13, $P<0.05$) and 2.27 ± 5 % (n=25, $P<0.05$) in astrocytes. In contrast, GB88 produced no significant effect on intracellular calcium levels in either neurons or astrocytes ($P<0.05$).

To investigate further the underlying mechanisms behind PAR2 activation, we performed internalisation studies using PAR2-YFP transfected tSA201 cells. PAR2 internalisation was evident following exposure to all PAR2 compounds that elevated intracellular Ca^{2+} levels. Strikingly, GB88 also led to PAR2 internalisation suggesting that GB88 may be a biased agonist. Moreover, we assessed the specificity of these PAR2 activators, no internalisation was observed in PAR1 and PAR4 transfected tSA201 cells.

Building on our data in CNS preparations and previous work revealing the neuroprotective effects of PAR2 activation, we aim to test the hypothesis that novel PAR2 activators are neuroprotective *in vitro* and *in vivo* models of neurological disorders. Determining the potential of PAR2 as a novel therapeutic for CNS disorders may provide new options for a large range of CNS diseases.

Poster Ref: P3-B-011

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Effect of mutations within the extracellular vestibule of the NMDA receptor channel on the inhibition by endogenous neurosteroids and implications for the receptor channel function.

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N-methyl-D-aspartate receptors (NMDAR) are glutamate-activated ion channels involved in excitatory synaptic transmission and synaptic plasticity. However their over activation leads to excitotoxicity which may underlie several neurodegenerative diseases. The activity of NMDAR can be influenced by various allosteric modulators including endogenous neurosteroid 20-oxo-5β-pregnan-3α-yl sulphate (pregnanolon sulphate; PAS) that inhibits responses of NMDAR in a use-dependent but voltage-independent manner. Previous attempts to identify the side of action for PAS on the NMDAR have so far failed. Our aim was therefore to identify amino acid residues on NMDAR that are important for the inhibitory effect of PAS using electrophysiological and molecular biological techniques in combination with molecular modelling.

We performed a series of double and single-point mutations in the TM1 and TM3 membrane domains of both GluN1 and GluN2B subunits. Results of these experiments show that inhibitory effect of negatively charged steroids at NMDAR was profoundly reduced in case of two mutations (T648A and A649T) within the highly conserved SYTANLAAF motif in TM3 of GluN1 subunit. In contrast, inhibition of these mutated NMDAR by positively charged steroids was voltage-dependent. Furthermore, GluN1(T648A)/GluN2B and GluN1(A649T)/GluN2B receptors showed to be spontaneously active and were insensitive to other inhibitors indicating that these mutations have considerably altered the receptor channel function.

These results suggest that extracellular vestibule of the NMDAR channel, which is accessible after receptor activation, is the site of action for neurosteroids with inhibitory effect and further have implications for the arrangement of the channel in the open configuration. We have used this to propose a model of the open state of the NMDAR channel. Detailed understanding of the mechanism of inhibitory action of neurosteroids on NMDAR has therapeutic importance for the development of drugs with neuroprotective effect.

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Poster Ref: P3-B-012

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Synaptome maps are altered in mouse genetic models of cognitive disorders.

Melissa Cizeron[1], Fei Zhu[1], Zhen Qiu[1], Mike Croning[1], Ellie Tuck[2], Kirsten M. Scott[3], Noboru H. Komiyama[1] and Seth G.N. Grant[1]

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Disruption of synapse proteins has been identified as the primary cause of many psychiatric and neurological diseases, including mental retardation, schizophrenia and autism spectrum disorders. Moreover, synapse loss highly correlates with cognitive decline in Alzheimer's disease (AD). Although proteomics allowed identification of over 1000 different proteins expressed at the synapse, the distribution of these proteins into different synapses in the brain has not been systematically evaluated, nor has the effect of mutations on this distribution. To address these issues we have developed methods to systematically map synaptic distribution of proteins and thereby generate synaptome maps (see Poster Zhu *et al.*; Qiu *et al.*).

We are using our new G2CSynMap method to assess potential synapse changes in various mouse models of brain diseases. G2CSynMap uses a combination of two state-of-the-art techniques: i) genetic labelling of the endogenous PSD95 protein using the green fluorescent protein eGFP; ii) high-throughput and high-resolution imaging to map individual synapses expressing the PSD95-EGFP fusion protein in entire coronal sections. We crossed mice expressing the PSD95-eGFP fusion protein with mouse mutants and systematically quantified synapse density and synapse features in hundreds of regions for several models of psychiatric and neurological diseases. We find increased expression of PSD95 in specific synapses of mice lacking either SAP102 or PSD93 proteins, which are paralogues of PSD95. In humans, mutations in the Dlg3 gene, encoding SAP102, cause non-syndromic mental retardation and de novo copy number variations in the Dlg2 gene, encoding PSD-93, have been identified in schizophrenia patients. Moreover, mice lacking SAP102 or PSD-93 proteins have specific cognitive deficits. Additionally, we observe local synapse loss around amyloid plaques, a pathological hallmark of AD, in TgCRND8/PSD95-eGFP mice, a model of AD disease overexpressing mutant human APP. These studies reveal i) that synaptome maps change in multiple models of human cognitive disorder, ii) paralogues of vertebrate genes regulate synaptome maps, iii) G2CSynMap is a versatile and powerful tool for studying and identifying vulnerable synapses and multiple disease mechanisms.

Poster Ref: P3-B-013

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Super-resolution imaging of genetically targeted PSD95 in the mouse brain.

Matthew Broadhead[1], Mathew Horrocks[2], Fei Zhu[1], Noboru Komiyama[1], David Fricker[3], Maksym Kopanitsa[3], Ruth Benavides-Piccione[4], Javier DeFelipe[4], Steven Lee[2] and Seth Grant[1]

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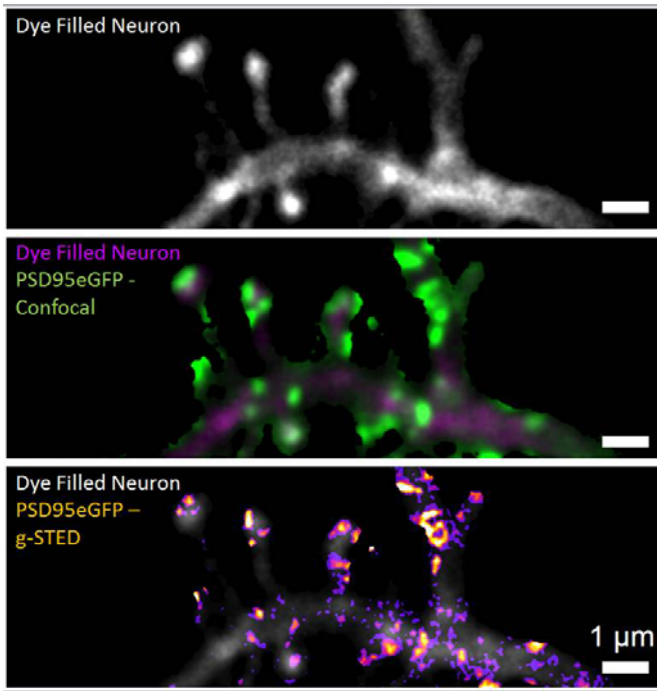
The postsynaptic proteome of excitatory synapses is comprised of a diverse set of proteins organised into multiprotein complexes. The subsynaptic organisation and distribution of these complexes is poorly understood, particularly *in vivo*. We have combined genetic labelling of a synaptic protein with quantitative super-resolution microscopy methods to resolve the organisation of key synaptic proteins in the mouse brain.

Two mouse lines expressing eGFP or mEos2 that are in-frame fused to the carboxyl terminus of the postsynaptic scaffold protein PSD95 were generated using homologous recombination in mouse embryonic stem cells. We used gated-stimulated emission depletion (g-STED) microscopy and photoactivatable localisation microscopy (PALM) to visualize endogenous PSD95 in fixed mouse brain sections from PSD95eGFP and PSD95mEos2 samples respectively.

Both imaging methods show that PSD95 was organised into discrete nanoclusters in all regions of the mouse hippocampus. Quantitative analysis shows that each synapse typically contains just one nanocluster, with some containing two or more. PALM shows nanoclusters are disc-like ellipsoids of 70 ± 30 nm (SD) in diameter. Surveying different regions of the hippocampus reveals the number of nanoclusters per synapse varies between distinct regions. Dye filling of individual neurons can be used to quantify the location and number of nanoclusters within a single dendrite.

These studies demonstrate that genetic labelling of endogenous synaptic proteins combined with super-resolution microscopy is a powerful approach to the study of synaptic protein expression and synaptic diversity *in vivo*. Our present findings suggest characteristic distribution of PSD95 into nanoclusters is a hallmark of synaptic diversity in excitatory synapses.



Poster Ref: P3-B-014

Theme: B: Molecular, Cellular and Synaptic Mechanisms

The role of NMDA receptors and synaptic plasticity in the induction and build-up of hippocampal gamma-frequency (30-80 Hz) oscillations *in vitro*.

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Network oscillations in the gamma band (30-80 Hz) have been extensively studied in the CA3 region of the hippocampus, with activity in this frequency range heavily implicated in cognitive processing, learning and memory. Persistent gamma-frequency oscillations can be evoked in CA3 by the cholinergic agonist carbachol (10 micromolar) *in vitro*. Interestingly, there is a gradual build-up of oscillatory power over 2-4 hours, after which oscillations remain stable for 1-2 hours. The mechanisms underlying this induction and build-up may be associated with synaptic plasticity, a process also widely associated with learning and memory. Two cellular mechanisms underlying synaptic plasticity, long-term potentiation (LTP) and long-term depression (LTD), involve glutamatergic NMDA and AMPA receptors, followed by activation of protein kinase A (PKA).

To investigate the association between synaptic plasticity and gamma-frequency oscillations, an NMDA receptor antagonist or PKA inhibitor was pre-incubated with slices prior to the induction of gamma oscillations by carbachol. Male Lister hooded rats were anaesthetised and intracardially perfused with artificial CSF, with slices then prepared as previously described in mice [1]. Slices were pre-incubated with NMDA receptor antagonist D-AP5 (100 micromolar) or PKA inhibitor H-89 (10 micromolar) for 60 and 90 minutes respectively. Carbachol was added and local field potentials recorded *via* microelectrode in CA3.

Pre-incubation with NMDA receptor antagonist D-AP5, or PKA inhibitor H-89, led to a faster induction of carbachol-induced gamma-frequency activity. These results indicate that NMDA receptors play an essential role in the build-up of persistent gamma-frequency oscillations. The effect of NMDA receptor antagonist pre-incubation on carbachol-induced gamma was similar to that seen with PKA blockade. This, in turn, suggests an interaction between synaptic plasticity, and the induction and build-up of carbachol-induced gamma oscillations.

1. J. E. Driver, C. Racca, M. O. Cunningham, S. K. Towers, C. H. Davies, M. A. Whittington, and F. E. LeBeau, 'Impairment of Hippocampal Gamma-Frequency Oscillations *in vitro* in Mice Overexpressing Human Amyloid Precursor Protein (App)', Eur J Neurosci, 26 (2007), 1280-8.

Poster Ref: P3-B-015

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Whole-brain mapping of excitatory synapses reveals molecular heterogeneity of PSD-95 and SAP102.

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Recent years have seen rapid progress in systematic brain mapping brain exemplified by several connectome studies1. Another fundamental and crucial complementary aspect to connectome studies is synaptome mapping2. However, to date a truly comprehensive atlas of synaptome that describes and charts excitatory synapses in all neurones across the entire mammalian brain is not yet available. Here we present for the first time a synapse map of the adult mouse brain, the G2CSynMAPP. Taking advantage of gene-targeting techniques, two major PSD (post synaptic density) scaffolding protein paralogues PSD-95 and SAP102 are in-frame fused with different fluorescent tags: enhance green fluorescent protein (EGFP) and monomeric Kusabira Orange2 (mKO2), respectively. By using a high-resolution, high-throughput spinning disk confocal microscope, we have established a standardized imaging platform and created a comprehensive and quantitative synapse atlas from the double knock-in fluorescent mice. A bespoke image analysis system is used to define synapse types and their distribution (see Poster Qiu *et al.*).

In normal adult brains, we observed characteristic sub-cellular distributions of tagged PSD proteins into distinct synapse types resulting in patterning at the level of the whole brain. Moreover, we observed patterning within anatomical regions, forming patches and gradients, reflecting an even greater level of diversity at individual synapse level. We are currently generating a catalogue of synapses that could help us understand the cause of this diversity.

Our results show for the first time the high degree of organization of excitatory synapses across the mammalian brain and give insights on its connectivity patterns, suggesting that discrete subpopulations of synapses might form the base of functional differences previously observed from PSD-95 and SAP102 knock-out mutant animals3-5.

Reference:

1. Oh *et al.*, Nature, 508(7495):207-14. 2014
2. DeFelipe *et al.*, Science, 330(6008):1198-201. 2010
3. Migaud *et al.*, Nature, 396(6710):433-9. 1998
4. Cuthbert *et al.*, Journal of Neuroscience, 27(10):2673-82, 2007
5. Nithianantharajah *et al.*, Nature neuroscience, 16(1):16-24, 2013

Poster Ref: P3-B-016

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Cloning a putative voltage gated sodium channel in the crayfish (*Astacus leptodactylus*).

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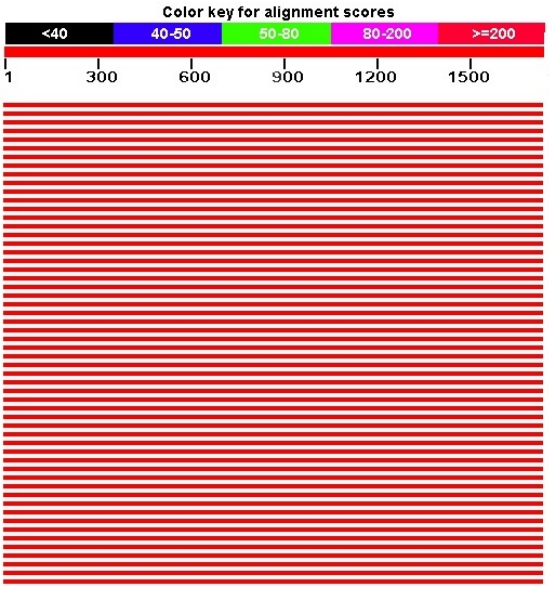
Crayfish preparations have widely been used as a model in various neuroscience experiments. Relatively less complex structure of the nervous system enabled many electrophysiological experiments which possibly could not be performed in any mammalian species. However, very few works is available for genes and genome of the crayfish. Further, even genes coding the ion channels, the most essential features of the nervous system, has not been explored yet. In the present work is firstly explored the sequence of gene coding a voltage gated sodium channel protein which is responsible for the rapid rise of the action potential, the unit signal in the nervous system. Since expression of sodium channel is an indicator of a nervous tissue, RNA samples were extracted from ganglia. cDNA samples were synthesised by using a reverse transcriptase PCR method. A set of degenerate primers were designed by considering conserved regions of known sodium channel genes among phylon species. Two different gene fragments have been amplified by using PCR and degenerate primers. Blast analysis of the sequence of the fragments revealed a high degree of similarity to the known sodium channels. Specific primers were designed and the missing parts between the fragments were amplified. Those efforts revealed a gene fragment 4900 bp in size. In order to clone the complete sequence, 5' and 3' ends of the target gene had to be identified. A rapid amplification of cDNA ends method has been employed to achieve the goal. Finally, complete sequence of a gene 5206 bp in size has firstly been cloned. The nucleotide sequence of the gene has been converted into amino acid sequence. When the amino acid sequence were compared to the known sodium channels, a 81 % similarity to the Cancer borealis sodium channel were determined. Hydrophobicity test of the putative sodium channel protein revealed four distinct domains possibly related to the four domains of a typical voltage gated sodium channel. Tissue specific expression pattern of the novel sodium channel gene has been identified by conducting a qPCR in cDNA samples from 9 different tissues. It was identified that the gene was expressed in ganglia and intestine but absent in the other tissues. (Grants: TUBITAK 113s555, HU BAB 13D031011003, 14D08101006).



Description	Max score	Total score	Query cover	E value	Ident
voltage-gated sodium channel [Cancer borealis]	2814	2907	99%	0.0	81%
voltage-gated sodium channel Nav1 alpha subunit [Periplaneta americana]	2383	2481	99%	0.0	71%
Sodium channel protein para [Zootermopsis nevadensis]	2377	2476	99%	0.0	69%
hypothetical protein TcasGA2_TC004749 [Tribolium castaneum]	2372	2554	99%	0.0	69%
para sodium channel [Blattella germanica]	2360	2459	99%	0.0	70%
PREDICTED: LOW QUALITY PROTEIN: sodium channel protein para-like [Bombus terrestris]	2358	2545	99%	0.0	70%
paralytic B [Tribolium castaneum]	2357	2539	99%	0.0	69%
para sodium channel [Blattella germanica]	2356	2455	99%	0.0	71%
sodium channel protein paralytic [Apis mellifera]	2355	2542	99%	0.0	70%
PREDICTED: sodium channel protein paralytic isoform X25 [Apis mellifera]	2355	2541	99%	0.0	70%
voltage-gated sodium channel alpha subunit isoform 1 [Nasonia vitripennis]	2354	2540	99%	0.0	70%
TPA: voltage-gated sodium channel alpha subunit [Nasonia vitripennis]	2353	2539	99%	0.0	70%

Analysis of sequence of the cloned voltage-gated sodium channel protein. Alignment and comparison of amino acid sequences (left). Calculated similarity indices of the cloned sodium channel to the other sodium channels in some other species (right). Obtained by using Blast function in NCBI web site.

Poster Ref: P3-B-017

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Do Aβ and tau act synergistically to drive synaptic degeneration Alzheimer's disease?

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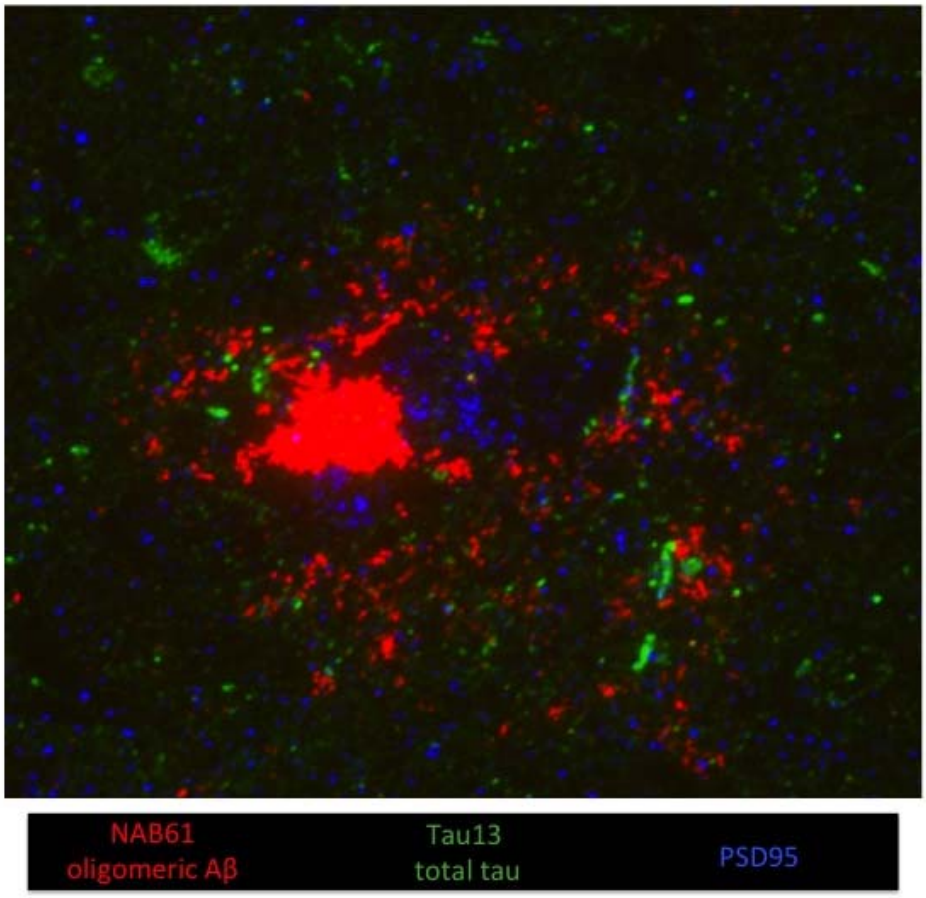
Synaptic degeneration is the strongest biological correlate of cognitive decline in Alzheimer's disease (AD). Both amyloid beta (Aβ) and tau proteins have individually been implicated in the synaptic degenerative process, however the interplay between these principal proteins remains elusive. Using a high resolution imaging technique called array tomography in postmortem samples of human brain tissue, we previously observed the accumulation of oligomeric Aβ at a subset of shrunken synapses. In mouse models, Aβ mediated synaptic changes have recently been shown to depend on tau, but whether these proteins converge at synapses in the human disease was previously unknown. In the present study we utilize array tomography to examine the subcellular localization of tau and Aβ. We observe a subset of both pre and postsynaptic terminals containing both oligomeric Aβ and tau, indicating that the cascade from amyloid to tau may occur at least in part in the synapse. The findings from this study are now to be extended to investigate the hypothesis that reducing tau levels will prevent synaptic degeneration in a novel mouse model of AD.



Imaging with Array Tomography. 70nm tissue sections are co-stained with antibodies against proteins of interest: oligomeric Aβ, total tau and synapses, pseudocoloured in red, green and blue, respectively. Imaging of serial sections with subsequent alignment and 3D reconstruction results in a highly resolved image where synaptic size, density and protein colocalisation can be analysed.

Poster Ref: P3-B-018

Theme: B: Molecular, Cellular and Synaptic Mechanisms

The effects of antiepileptic drugs on susceptibility to seizure-like-events in hippocampal-entorhinal slices prepared using standard and sucrose based artificial cerebrospinal fluid.

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[1]Aston University, [2]Newcastle University

The brain slice preparation can be used to address a wide variety of questions regarding electrophysiological and pharmacological responses. Since Henry McIlwain's pioneering work in the 1950's, various improvements have been made to brain slice preparations in order to better preserve the brain. A common protocol of brain slice preparation requires decapitation and removal of the brain into normal artificial cerebrospinal fluid (StdACSF). Alternatively, a terminal dose of anesthesia can be administered after which a cardiac perfusion with sucrose based aCSF (sACSF) can be carried out. SACSF prepared slices have previously been shown to preserve interneurons and maintain high levels of GABA mediated inhibition (see Hazra et al, 2015 at this meeting). The current study investigated how variations in slice preparation alter the susceptibility to seizure-like-events and their response to antiepileptic drugs (AEDs).
Following application of Mg2+ free aCSF, significantly more StdACSF prepared slices (>80%, n = 13/16) demonstrated ictal-like events, in comparison to (sucrose-perfused) sACSF slices (<35%, n = 5/16). Slices which demonstrated ictal-like events were treated with multiple AEDs. Almost all seizure-like events could be abolished in the StdACSF preparation (>80% n = 11/13), however, by comparison the sACSF preparation was much less sensitive to AEDs (<60% n = 3/5). Interestingly, if we exposed sACSF slices to low magnesium, high potassium aCSF perfusate, a high proportion of slices (>90% n = 15/16) demonstrated seizure-like events, and these events were highly responsive to AEDs (>80%, n = 13/15), in a similar manner to standard aCSF prepared slices. These findings suggest that variations in slice preparation and post-preparation treatment affect susceptibility to seizure-like-events and their response to AEDs.

Poster Ref: P3-B-019

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Cloning and determination of tissue specific expression pattern of *Astacus leptodactylus* Na^+ / Ca^{2+} exchanger gene.

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Cytosolic Ca^{2+} plays an essential role in various cellular functions. Changes in cytosolic Ca^{2+} concentration is important for different cellular activities like muscle contraction and neurotransmitter release. A set of channels and exchangers are responsible for maintenance of resting calcium concentration and the generation of the calcium transient. Na^+/Ca^{2+} exchanger can move Ca^{2+} in either direction depending on net electrochemical driving force acting on the exchanger. Structure and function of Na^+/Ca^{2+} exchanger is conserved within the animal kingdom. In the crayfish there are some recent functional studies indicating the presence of Na^+/Ca^{2+} exchanger. However, there is no report focusing onto genetic and molecular properties of the crayfish exchanger yet. To explore the nucleotide sequence of the crayfish Na^+/Ca^{2+} exchanger gene, various molecular techniques have firstly been employed. The homology observed among closely related species have been considered while constructing degenerate primers to amplify the target gene in PCR. As a result, the complete coding sequence of the putative crayfish Na^+/Ca^{2+} exchanger gene has been revealed. Corresponding amino acid sequence has been found to be 58 – 65 % similar to the other known Na^+/Ca^{2+} exchangers, indicated that the sequence may belong to the exchanger protein family. Analysis of the amino acid sequence indicated two transmembrane domains flanking a large intracellular loop. Computational analysis for hydrophobicity and transmembrane segments revealed that N- terminal of the peptide is extracellularly located. Initial and terminal domains are both consisted of 5 transmembrane segments. By using specific primers and qPCR method, tissue specific expression pattern of crayfish Na^+/Ca^{2+} exchanger gene has been established. The results indicated that in the crayfish the exchanger is expressed in excitable or biologically active tissues like ganglia, muscle and antennal gland while its expression is almost absent in gill which passively filters the neighboring fluid. Future efforts will be dedicated to define structure-function relationship of the discovered gene.

Supported by TÜBİTAK (grant #113 S 555), TÜBİTAK BIDEB 2210 and Hacettepe University Research Foundation (grant #014D08101006 and #013D03101003)

Poster Ref: P3-B-020

Theme: B: Molecular, Cellular and Synaptic Mechanisms

N-glycosylation regulates the trafficking of NMDA receptors.

Kristyna Skrenkova[1], Katarina Lichnerova[1], Martina Kaniakova[1], Seung Pyo Park[2], Ya-Xian Wang[3], Ronald S. Petralia[3], Young Ho Suh[2] and Martin Horak[1]

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N-methyl-D-aspartate receptors (NMDARs) are a subclass of glutamate receptors which are essencial for the excitatory neurotransmission in the mammalian brain. The surface and synaptic numbers of the NMDARs are regulated at multiple levels including their early processing within the endoplasmic reticulum (ER) due to the presence of the ER retention and export signals and by their posttranslational modifications. However, the role of very common posttranslational modification, N-glycosylation, in the regulation of the NMDARs has not been studied in detail. Using complex approach including biochemistry, confocal and electron microscopy and electrophysiology in the conjunction with the lentiviral-based molecular replacement strategy in the mammalian cell lines and neurons, we showed that the major types of the NMDARs, the GluN1/GluN2A and GluN1/GluN2B, are efficiently released from the ER only when two asparagines within the GluN1 subunit are N-glycosylated. Furthermore, we did not observe major effect of the N-glycosylation on the functional properties of the NMDARs receptors. Our deglycosylation and lectin-based biochemical analysis revealed that native NMDARs contain likely only the basic, mannose and hybrid types of the N-glycans, in contrast to the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs), which likely contain also the complex types of the N-glycans. Our findings identify novel role of the N-glycosylation in the regulation of the functional NMDARs on the cell surface including excitatory synapses.

This work was supported by the project from the Grant Agency of the Czech Republic (14-02219S; M.H.).

Poster Ref: P3-B-021

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Interaction of the vesicle priming protein Munc13-1 with the Ca^{2+} sensor Doc2B controls Gq-protein coupled receptor-mediated short-term potentiation of exocytosis.

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Department of Biomedical Sciences, University of Sheffield

G protein-coupled receptor (GPCRs) signaling pathways are part of a complex information processing system that modulates transmitter release from neurons and neuroendocrine cells. Given the fact that aberrant GPCR signaling and transmitter release is associated with numerous disorders and diseases, it is surprising how little we known about the interplay between these receptors and the exocytotic machinery.

Phospholipase C (PLC)-coupled GqPCRs for example strongly potentiate exocytosis. They activate PLC to hydrolyze phosphatidylinositol-4,5-bisphosphate (PIP2) into the two prominent second messenger diacylglycerol (DAG) and inositol-1,4,5-trisphosphate (IP3). IP3 mobilizes Ca^{2+} from stores and DAG controls numerous cellular functions by regulating C1-domain-containing proteins such as the vesicle priming protein Munc13-1. We showed before that a DAG-binding deficient Munc13-1 mutant (Munc13-1H567K) completely abolishes GqPCR-mediated potentiation of exocytosis in neuroendocrine chromaffin cells. This potentiation also requires IP3-mediated Ca^{2+} release from stores but the molecular target of Ca^{2+} is unidentified. Doc2B is a high affinity calcium-binding protein known to interact with Munc13-1 and may therefore play a role in GqPCR-mediated potentiation.

Using live cell imaging we show here that activation of GqPCRs caused the simultaneous translocation of Munc13-1 and Doc2B to the plasma membrane. Neither Munc13-1 nor Doc2B translocation dependent on Doc2B/Munc13-1 interaction as revealed by a mutant Doc2B that no longer binds to Munc13-1 (Doc2BM13). While Munc13-1 translocation was prevented by inhibiting PLC or by Munc13-1H567K, Doc2B translocation entirely relied on Ca^{2+} release from stores. Combining voltage-clamp recordings with high-resolution membrane capacitance measurements in conjunction with the Doc2BM13 mutant clearly showed that Doc2B/Munc13-1-interaction was required for GqPCR-mediated potentiation of exocytosis.

In summary, we demonstrate how signal integration leads to potentiation of exocytosis. We found that GqPCRs use both branches of their signaling cascade to recruit Munc13-1 and Doc2B independently to the plasma membrane. There the Doc2B/Munc13-1-interaction then is crucial for GqPCR-mediated vesicle priming to potentiate exocytosis.

Poster Ref: P3-B-022

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Neuronal activity mediated regulation of glutamate transporter GLT1 surface diffusion in astrocytes.

Sana Al Awabdh, David Sheehan, James Muir, Rosalind Norkett, Alison Twelvetrees and Josef Kittler
University College London

Controlling the extracellular concentration of glutamate in the brain is crucial for normal signalling and to prevent neurotoxicity. The astrocytic excitatory amino-acid transporter 2 (EAAT2, GLT1) is the major glutamate transporter for clearing synaptic glutamate. However, little is known regarding the mechanisms that regulate surface dynamics of GLT1. Modulating GLT1 surface diffusion to alter its number in apposition to activated synapses could play a key role in regulating local glutamate uptake or buffering to modulate glutamate clearance and synaptic activity. Here, we have used live cell imaging to study the mechanisms regulating GLT1 surface diffusion in the membrane of astrocytes cultured alone or maintained in co-culture with neurons. We show a rapid and reversible dispersal of surface GLT1 clusters upon glutamate treatment, correlating with an increase in GLT1 surface mobility. Blocking the transporter activity prevented this glutamate-dependent dispersal. By using single particle tracking, we showed that GLT1 is highly dynamic and, remarkably, more mobile in the presence of neurons. Interestingly, the two main GLT1 C-terminal isoforms expressed in the adult brain, Glt1a and Glt1b, are both found to be stabilised in apposition to synapses, with GLT1b is more so under basal conditions. Furthermore, alteration in neuronal activity *via* pharmacological treatment modulates the dynamics of GLT1a and GLT1b. Altogether, these data reveal that the astrocytic GLT1 surface mobility is modulated during neuronal activity, which may play a key role in shaping glutamate clearance and glutamatergic synaptic transmission.

Poster Ref: P3-B-023

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Arc directly interacts with clathrin-adaptor proteins to facilitate AMPAR endocytosis.

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[1]University of Bradford, [2]University of Sao Paulo, Brazil [3]University of Warwick

Activity-regulated cytoskeleton (Arc) is a neuron-specific immediate early gene required for learning and memory. As such, Arc protein expression is critical for several forms of synaptic plasticity by facilitating endocytosis of AMPA receptors (AMPAR). To map the steps linking Arc expression to endocytosis of AMPAR, we immunoprecipitated endogenous Arc from C57BL/6 mouse hippocampal lysates and identified unknown clathrin-adaptor proteins (CAP) as Arc-binding patterns. To characterize the Arc/CAP interaction we used several strategies: a) Arc co-IPs with components of the CAP in hippocampal lysates from adult C57BL/6 mice, b) recombinant Arc directly binds to the GST-containing the CAP. To determine the Arc sequence that mediates the Arc-CAP interaction, we generated Arc mutants with successive deletions from either the Nt or Ct and performed GST pull-down assays c) to determine the subcellular location of the Arc/CAP interaction we used bimolecular fluorescent complementation assays combined with confocal microscopy.
To test whether Arc regulates AMPAR endocytosis *via* the interaction with newly identified CAP, we recorded AMPAR-mediated miniature excitatory postsynaptic currents (mEPSCs) from primary hippocampal cultures (PHCs) at 15-18 days *in vitro*. PHCs co-expressed microRNAs-eGFP-tagged to knockdown the CAP with either Arc-wild-type (Arc-WT) or Arc-mutants, which do not interact with the endocytic machinery. miRNA sequences predicted not to target any known vertebrate gene were used as negative controls. The decrease in AMPAR-mediated mEPSC amplitude observed in PHC expressing Arc-WT is reduced in cells expressing Arc-mutants, suggesting that the Arc-dependent endocytosis of AMPAR requires interaction with the CAP. As expected, the increase in AMPAR-endocytosis promoted by Arc was reduced in cells where the expression of the CAP was depleted. Furthermore, disruption of the Arc/CAP interaction, by depleting the expression of CAP, dampens the Arc-mediated reduction in synaptic strength observed in homeostatic synaptic downscaling.

Our discovery that Arc directly binds directly to clathrin-adaptor proteins provides the crucial mechanistic link explaining how activity-dependent expression of Arc regulates synaptic plasticity, learning and memory formation.

Poster Ref: P3-B-024

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Decreased GABAergic synaptic strength in midbrain dopamine neurons in spontaneously hypertensive rats compared to Wistar-Kyoto rats.

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MRC Clinical Sciences Centre, Imperial College London

The spontaneously hypertensive rat (SHR) has been used extensively to identify genes underlying a number of metabolic phenotypes. In addition, these rats are hyperactive and impulsive, and it has been suggested represent a model of attention-deficit hyperactivity disorder (ADHD). These behavioural features, and ADHD, are commonly associated with dysfunction of the dopamine system. However, little is known about dopamine neuron properties in SHRs (or in control Wistar-Kyoto rats (WKYRs)). We have, therefore, conducted whole-cell electrophysiological recordings from midbrain dopamine neurons in acute brain slices from these two rat strains, together with single-cell morphological reconstructions and immunostaining. Spontaneous firing activity, action potential waveform characteristics, and maximal firing rate in response to depolarisation, were all similar in both strains. In addition, excitatory glutamatergic synaptic activity appeared similar in both strains. However, we observed significantly lower amplitude and frequency of miniature inhibitory GABAergic synaptic currents (mIPSCs) in SHRs compared to WKYRs. Evoked IPSC paired-pulse ratios and the coefficient of variation of evoked IPSC amplitude were the same in both strains, suggesting that there are no differences in presynaptic GABA-release, and that the differences we observed in mIPSC frequency and amplitude may be postsynaptic. The digital reconstruction of individual dopamine neurons filled with neurobiotin showed that dendritic structure was similar in both strains. In contrast, immunostaining showed that the expression level of the postsynaptic marker gephyrin appeared to be reduced in SHRs compared to WKYRs. Taken together, these findings suggest that GABAergic synaptic strength is reduced in SHRs, which may in turn lead to dopaminergic hyperactivity, and consequently behavioural hyperactivity.

Poster Ref: P3-B-025

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Fine processes of radial glia-like stem cells in the hippocampal adult neurogenic niche ensheath local synapses and vasculature.

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Situated in the dentate gyrus of the hippocampus is a neurogenic niche, capable of supplying new neurons to the region throughout adult life. These new neurons integrate into the circuitry of the hippocampus as they become fully-functional mature granule cells. They divide and differentiate from a self-renewing population of radial glia-like (RGL) stem cells, the cell bodies of which reside in the subgranular zone. Although the process of adult neurogenesis is highly regulated by the neurogenic niche, relatively little is known about the cellular contacts established by the RGL stem cells. The RGL stem cells have a curious morphology; they extend a large radial process across the granule cell layer, then finer processes proliferate at the border of the molecular layer. We used correlative light and electron microscopy to examine how these fine processes interact with their environment, with a view to understanding why they possess this particular morphology.

We used Nestin-GFP transgenic mice to label the Nestin-expressing RGL stem cells with either immunogold or immunoperoxidase methods. To describe the overall structure of an individual RGL stem cell, we used serial block-face scanning electron microscopy to capture aligned images of an immunoperoxidase-labelled cell, then reconstructed the cell in three dimensions. To focus on individual features from multiple RGL stem cells, we selected regions of interest with light microscopy, captured images of these regions using transmission electron microscopy and reconstructed labelled structures in three dimensions.

Analyses revealed that RGL stem cells send major processes toward blood vessels situated in the inner molecular layer, wrap them with thin sheets, and share their surface area contact with local astrocytes. The RGL stem cell processes also branch into finer strings, consisting of mitochondria-containing varicosities, from which individual processes extend towards local asymmetrical synapses. This intimate relationship of the RGL stem cell with both neuronal and vascular components of the local environment, suggests that it may be receiving signals to aid its survival or to activate the production of new neurons.

Poster Ref: P3-B-026

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Neuropeptide Y neurons represent a distinct glucose-sensing population in the nucleus of the solitary tract.

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Appropriate glucose homeostasis is essential for survival and the brain comprises specified neurons that can detect and respond to blood glucose fluctuations. Some of these neurons, such as those in the hypothalamic arcuate nucleus and the lateral hypothalamic area (LHA), express neuropeptide Y (NPY) and have been previously shown to be glucose inhibited. Within the Nucleus of the Solitary Tract (NTS) in the brainstem, a brain structure known to contain neurons that are glucose-sensitive and important to the integration of peripheral energy signals, there exists a population of neurons that express Neuropeptide Y. However, their glucose-sensing ability is presently unidentified. In the present study, we investigated how NTS-NPY neurons would respond to changes in glucose availability. The present study employed mice expressing green fluorescent protein under the control of NPY regulatory elements and here show neurochemical and electrical properties of how these neurons respond to challenges of *in vivo* fasting and insulin-induced hypoglycemia, and *in situ* electrical responses to changes in extracellular glucose. C-fos measurements showed an increase of co-localization with certain subpopulations of NTS-NPY neurons activated during these challenges. We also observed this activation during electrophysiological measurements where elevated extracellular glucose induced a membrane hyperpolarization in ~ 40% of NTS-NPY neurons *in situ*. The present data suggest that in the NTS there is an NPY-expressing neuronal subpopulation that can respond to glucose fluctuations thereby expanding on our understanding of how brain circuitry regulates glucose homeostasis. This work was funded and supported by the Wellcome Trust.

Poster Ref: P3-B-027

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Further insights into the synaptic function of tau protein.

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The microtubule associated protein tau is a principal component of Alzheimer's disease (AD) pathology (1) and is now also known to be required for the induction of long-term depression (LTD) of synaptic transmission in the hippocampus (2). Using a combination of biochemical and electrophysiological approaches, we have further probed the role of tau in synaptic function. We find that an AMPA receptor (AMPAR) internalization mechanism is impaired in tau KO mice and that tau-shRNA transfected neurons have enhanced AMPAR-mediated current at extrasynaptic sites of AMPAR turnover (3). LTD stimulation was found to cause selective phosphorylation of tau at serine 396 and 404 residues, but not at serine 202 or threonine 205 residues. Remarkably, preventing phosphorylation at serine 396 specifically impaired LTD, suggesting a critical role for this residue in the regulation of synaptic tau function. Finally, we show that tau KO mice exhibit deficits in spatial reversal learning. These findings underscore the physiological role for tau at the synapse and identify a behavioural correlate of its role in LTD. These findings could also have important implications for the dysregulation of synaptic plasticity in AD (4).

References

1. Kowall, N. & Kosik, K. (1987). Axonal Disruption and Aberrant Localization of Tau Protein Characterize the Neuropil Pathology of Alzheimer's Disease. Ann Neurol. 22, 639–643.

2. Kimura, T. *et al.* (2014). Microtubule-associated protein tau is essential for long-term depression in the hippocampus. Phil. Trans. R. Soc. B 369, 20130144.

3. Ashby, M. C. *et al.* (2004). Removal of AMPA receptors (AMPARs) from synapses is preceded by transient endocytosis of extrasynaptic AMPARs. Journal of Neuroscience, 24, 5172–5176.

4. Shankar, G. M. *et al.* (2008). Amyloid-β protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. Nat Med 14, 837–842.

Poster Ref: P3-B-028

Theme: B: Molecular, Cellular and Synaptic Mechanisms

GABA-B receptor function in healthy volunteers, a pharmacokinetic and pharmacodynamic study of two doses of baclofen compared to placebo.

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Recent evidence suggests a role for the γ-aminobutyric acid type B (GABA-B) receptor agonists in addiction and its treatment, however characterization of this receptor system in clinical addiction is limited. In particular it is unclear why some but not all patients tolerate or require high doses for their alcoholism. The current pharmacokinetic and pharmacodynamic study was designed to assess the effects of the GABA-B agonist, baclofen, on brain function in healthy volunteers. The findings from this study will be used to inform future studies investigating the sensitivity of GABA-B receptors in alcohol and opiate addicts.

Eight healthy male volunteers completed a double blind randomised 3-way cross over study, receiving oral placebo (vitamin C 100mg), 10mg and 60mg baclofen with an interval of at least 1 week between each study day. Subjective and objective measurements were taken at baseline (before medication) and at +30mins, 1, 2, 3, 4 and 6 hours after dosing. Objective measures included blood samples for analysis of plasma baclofen levels, heart rate and blood pressure. Participants completed a number of subjective rating scales including: - the Subjective High Assessment Questionnaire (SHAS), visual analogue scales for sleepy, relaxed, tense and alert and a drawing task assessing motor coordination (zig-zag task).

For the high dose, changes in subjective and objective variables compared with baseline reached a peak at 2 hours post dosing compared with placebo. Changes after the low dose were less evident. Subjective data indicates a significant increase ($p<0.05$) in total SHAS scores and in individual items including feeling ‘drunk or intoxicated’, ‘effects of alcohol’ and ‘muddled or confused’, at 2 hours after the high dose, compared with placebo. Systolic blood pressure was also increased at the 2 hour time point after the high dose, compared with placebo values.

Changes in these pharmacodynamic parameters will be presented in relation to pharmacokinetic data obtained using liquid chromatography mass-spectrometry (LC-MS) to measure plasma baclofen concentrations. As part of this pilot study plasma baclofen analysis techniques have been developed to optimise accurate assessment of plasma baclofen levels.

Poster Ref: P3-B-029

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Effect of the M1/M4-muscarinic receptor agonist, xanomeline, on synaptic activity in the mouse brain.

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The M1 muscarinic receptor is highly expressed in the hippocampus and is involved in plasticity and memory (Buchanan, 2010; Anagnostaras, 2003). Here we use a prion-model of neurodegeneration (Rocky Mountain Laboratory or RML mice) to test the effects of the M1/M4-selective agonist, xanomeline, on fear learning in wild-type and prion-infected mice. In wild-type mice, fear conditioning (FC) triggers activation of markers of neuronal activity and plasticity, c-Fos and ARC, in hippocampal CA1- CA3 regions and the dentate gyrus. The M1 receptor becomes activated during a fear learning process, as phosphorylation at serine 228 is increased in overlapping regions of the hippocampal formation following FC. In RML mice, for which cognitive decline is strongly correlated with loss of presynaptic terminals (Cunningham, 2003), FC does not trigger c-Fos expression and fear learning is impaired compared to control mice. However, in the presence of xanomeline, c-Fos is strongly activated and cognitive functions are restored, pointing to a major role of M1 receptor in fear learning in prion mice. Investigation of the electrophysiological properties of CA1 neurons obtained in acute brain slices of RML mice, show that xanomeline acts to decrease neuronal excitability (IV curve relationship, action potential characteristics and spontaneous glutamatergic transmission). As the regulation of post-synaptic AMPA receptors is critical for the synaptic changes underlying learning and memory, we hypothesize that the M1 receptor may regulate AMPA receptors activity through trafficking and/or modulation of the receptor's channel properties. Indeed phosphorylation of the GluR2 but not GluR1 subunit in the hippocampus is differentially regulated by xanomeline. These data show that the M1 muscarinic receptor is implicated in fear learning and memory and that the agonist xanomeline can rescue the cognitive deficits in a model of neurodegenerative disease by regulating hippocampal neuronal activity and synaptic plasticity.

Funding: Eli Lilly Lift/Larp grant and MRC programme run.

Poster Ref: P3-B-030

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Effects of the benzofuran 5-MAPB (1-(benzofuran-5-yl)-N-methylpropan-2-amine) on dopamine release in rat nucleus accumbens.

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5-MAPB (1-(benzofuran-5-yl)-N-methylpropan-2-amine) is a novel “legal high” structurally related to other designer drugs such as 5- and 6-APB and MDMA. It has been banned in the UK in 2013 and subsequently listed in class B drug together with similar benzofuran entactogen [1]. Although some researchers suggest a preferential activity on serotonin reuptake transporters (based on users’ experience), little is known about its pharmacological properties. Moreover, a recent study has demonstrated that 5-APB, a de-methylated version of 5-MAPB, slowed dopamine (DA) reuptake and caused reversal of dopamine transporter (DAT) [2]. On these premises, we have investigated the potential effects of 5-MAPB on dopamine efflux in the nucleus accumbens, a brain region involved in reinforcement and addiction mechanisms. In particular, we evaluated: 1) the binding of 5-MAPB to DAT, by assessing its ability to displace the selective DAT-radioligand [125I]RTI-121; 2) the effects of 5-MAPB on electrically-evoked DA efflux measured by fast cyclic voltammetry (FCV) in rat brain slices, by measuring peak DA efflux and time-constant of the dopamine reuptake half-life.

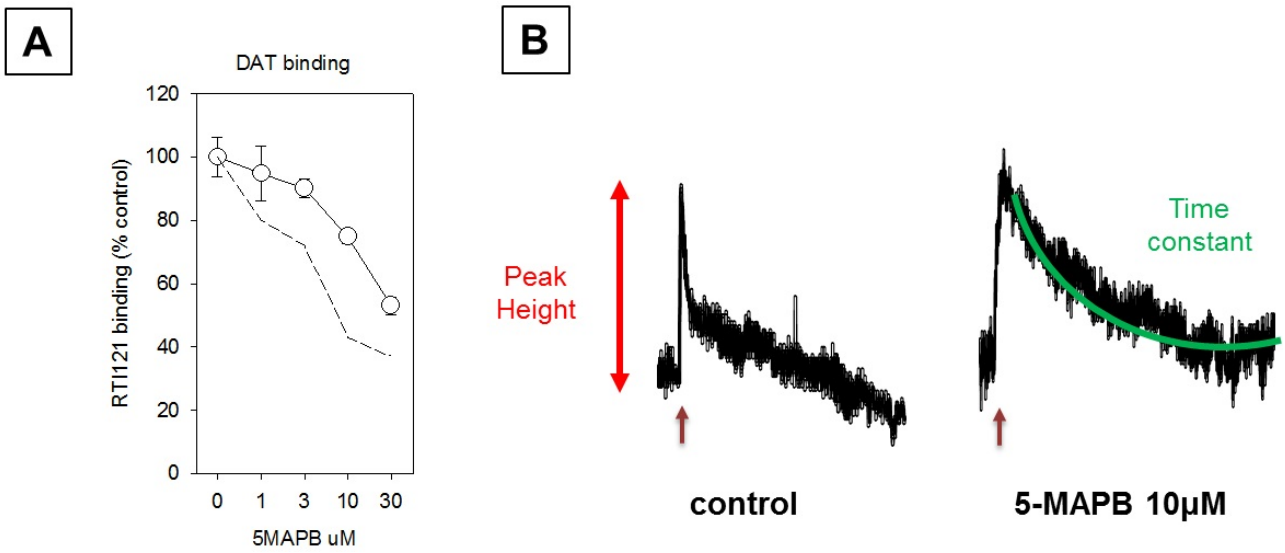
Binding assays demonstrated that increasing concentrations of 5-MAPB (0-30 μM) reduced 125I-binding in a concentration dependent manner, thus indicating competition between 5-MAPB and RTI-121 for the DAT. We also show cocaine displacement of RTI-121, which was slightly greater than 5MAPB. In FCV experiments, superfusion of accumbens slices with different concentrations of 5-MAPB (0.1-10 μM) did not modify electrically-evoked peak DA efflux (101±5% of baseline levels at 10 μM). In contrast, 5-MAPB dramatically increased time-constant, showing a ~10-fold increase compared to basal level at the highest concentration tested (10 μM).

Taken together, these data provide the first evidence of 5-MAPB pharmacology, confirming its suspected affinity at the DAT and we provide functional data of DAT inhibition. These data also suggest potential addictive risk related to its abuse.

References

1.UK Home Office (2014-03-05). "The Misuse of Drugs Act 1971 Order 2014". UK Government. Retrieved 2014-03-11.

2.Dawson *et al.* Prog Neuropsychopharmacol Biol Psychiatry. 2014;48:57-63.



A) Concentration-response curve for [125I] RTI121-displacement by 5-MAPB (open circles) and cocaine (dashed-line).B) Representative traces showing electrically-evoked dopamine efflux at baseline (left) and after 60 min superfusion with 5-MAPB 10 µM (right). Upward arrow shows local electrical stimulation (10 pulses at 100 Hz).

Poster Ref: P3-B-031

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Using iPSC-derived cortical neurons to increase integrin expression in the CNS.

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Regeneration of the adult CNS is one of the most challenging questions facing neuroscientists today. Repair of mature neurons is limited largely due to two factors: the growth-inhibiting environment created after injury and the innate inability of CNS neurons to regenerate. Integrins, a family of heterodimeric cell-surface receptors, have been implicated in regeneration in both the peripheral and central nervous systems. Within the nervous system they are involved in cell-cell and cell-matrix signalling, allowing extracellular matrix molecules to communicate with cytoskeletal components. Literature suggests integrins are important for growth cone formation, neurite outgrowth and axon regeneration. During development, integrin expression is high to assist in axonal elongation. However, this level of expression declines with age resulting in reduced plasticity and growth. Research indicates that increasing integrin expression can promote axonal regeneration. More recent work, however, has shown that exogenously-expressed integrins are not efficiently transported within adult CNS axons. In order to address this CNS deficit, we have examined the use of human iPSC-derived (induced pluripotent stem cells) to drive the expression of integrins in the adult CNS. Using a combination of western blotting and immunofluorescence techniques, we determined the endogenous expression level of integrin within human iPSC-derived cortical neurons. To assess survival of human iPSC-derived cortical neurons in rodent CNS, neonatal cortical grafting of human NPCs (neural progenitor cells) was carried out. Using specific coordinates, NPCs were injected into layer V of the sensorimotor cortex of postnatal day 0 Sprague Dawley rats. Following grafting, animals were perfused at the following time points post-transplantation: 2, 4, 6 and 8 weeks. Transplant survival was analysed using immunofluorescence for human-specific markers. In these cases, we have observed cell survival and the extension of axonal projections up to 6 weeks post-transplantation.

Poster Ref: P3-B-032

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Analysis of axonally localized mRNAs from human stem cell-derived glutamatergic neurons.

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Axonal translation is necessary during growth cone guidance, synaptogenesis and many forms of synaptic plasticity, producing changes in the local proteome. We do not know the relative contribution of local translation to the spatiotemporal composition of these protein microdomains, such as the presynapse. Many axonal mRNAs have been identified in model organisms but not human cells. Human embryonic stem cell derived neurons (hESC-neurons) provide a unique and convenient method to access human axons. Using glutamatergic hESC-neurons grown in axon-isolating microfluidic chambers we performed microarray gene expression analysis on axonally localized RNA as well as whole cell RNA. Almost 4000 transcripts were more than 1.5 fold enriched in axons compared to whole cell and a slightly smaller number were more than 1.5 fold enriched in the global whole cell transcriptome than in axons. These enriched populations represent different gene ontology categories; the axonal transcripts encode secreted and extracellular proteins as well as cation and voltage-gated channels while the whole cell transcripts encode intracellular and nuclear proteins involved in chromosome organization and DNA repair. Transcripts that are reliably localized to hESC-neuron axons are functionally similar to transcripts reliably localized to primary rat cortical neurons. Further, when we compared the axonal transcriptome of hESC-neurons to three published axonal transcriptomes from ex vivo rat peripheral and central nervous system neurons we found 21 conserved mRNAs across the four datasets, including B-actin, Gap43 and Calmodulin 2. To estimate the contribution of axonal translation to the presynaptic proteome we compared the four transcriptome datasets to proteins detected in purified synaptosomes and found that on average 15% of presynaptic protein transcripts are axonally localized across all four transcriptomes. In conclusion, differential gene expression between compartments of polarized neurons likely reflects the capability local translation to regulate local function. Characterizing conserved and unique axonal transcripts between neuron types will bring us closer to understanding the role of axonal translation in normal brain function as well as in disease.

Poster Ref: P3-B-033

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Investigating the pharmacogenetics of citrus and green tea flavonoids in a simple model system.

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Flavonoids are a large family of naturally occurring compounds that provide important health benefits, yet the molecular mechanisms underlying their effects remain unclear. Many studies have suggested that the mechanism of action of flavonoids in these health-promoting effects are through an antioxidant activity, however recently studies have also suggested that they may act through direct modulation of cell signalling.

The social amoeba, *Dictyostelium discoideum*, is a simple non-animal model that has been widely used to investigate how compounds work at a molecular level in relation to health and disease. A range of compounds have been analysed using this model including the flavonoid naringenin and the epilepsy treatment valproic acid. The model provides distinct parts of the life cycle for growth and development, and can be used for studies relating to acute (cell behaviour) or chronic (developmental) effects. In this study, *D. discoideum* has been used to investigate the mechanisms of three widely found flavonoids: epicatechin (EC), epigallocatechin gallate (EGCG) and hesperetin. Growth assays have been conducted using a range of micromolar concentrations on *D. discoideum* and indicate a dose-dependent response on growth inhibition. We show that EC and EGCG have a maximal effect of 70% growth inhibition at 400 uM whereas hesperetin is more potent and causes 95% growth inhibition at 200 uM. Growth curve analysis has enabled IC50 calculation for EC, EGCG, and hesperetin: 18.9 uM, 8.84 uM, 6.49 uM respectively. Development assays show that these compounds have no effect on fruiting body formation at concentrations 20x the IC50 and do not have an acute effect on cell behaviour. These results indicate that flavonoids may modulate proteins involved in *D. discoideum* growth (cellular division and cytokinesis), and have enabled ongoing genetic screens to identify the primary site(s) of action of EC, EGCG, and hesperetin through reverse genetics using a library of insertional mutants.

Our data demonstrates that D. discoideum has potential as a simple model to identify the molecular targets of EC, EGCG, and hesperetin in humans, to provide insight into the specific signalling pathways flavonoids regulate in a range of beneficial health effects.

Poster Ref: P3-B-034

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Increasing fatty acid amide hydrolase substrates attenuates TLR4-induced neuroinflammation independent of central cannabinoid receptor activation.

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Introduction: Enhanced endocannabinoid tone modulates neuroinflammatory responses and thus may provide a potentially novel therapeutic target for neurodegenerative and psychiatric disorders. Accordingly, recent data have demonstrated that inhibition of the anandamide (AEA) hydrolytic enzyme FAAH, attenuates neuroinflammatory responses following TLR3 or TLR4 activation1 2. However, the precise receptor mechanisms underpinning these effects are not fully elucidated. This study examined if attenuation of TLR4-induced neuroinflammation following FAAH inhibition was mediated by endocannabinoid receptor targets within the brain.

Methods: Rats received acute microinjection of the CB1 receptor, CB2 receptor, PPARγ or PPARα antagonist (AM251, AM630, GW9662 or MK886, respectively), 15 minutes prior to systemic administration of the FAAH inhibitor PF3845. Thirty minutes post PF3845; animals received systemic administration of LPS and were sacrificed 2h later. Frontal cortical tissue was excised and expression of NFkB-inducible inflammatory genes was determined using qRT-PCR. Concentration of AEA, PEA and OEA were determined using LC-MS-MS. MAPK/ERK activation was examined using western immunoblot analysis. Data were analysed using one-way ANOVA followed by Fisher's LSD post-hoc test or unpaired two-tailed t-test. $p < 0.05$ was deemed significant.

Results: PF3845 increased AEA, PEA and OEA levels in the frontal cortex, an effect associated with an attenuation of LPS-induced increases in expression of IkBα and NFkB-inducible genes IL-1β, IL-6, TNFα and IL-10. Central administration of AM251, AM630, GW9662 or MK886 failed to affect the PF3845-induced attenuation of cytokine expression following LPS. Furthermore, PF3845 failed to alter pERK1/2 expression compared to vehicle-LPS counterparts.

Summary & conclusion: Increasing FAAH substrate levels in the brain potently attenuates TLR4-induced neuroinflammatory responses. These effects do not appear to be mediated *via* activation of central cannabinoid receptors or PPARs. Further research is required in order to decipher the central receptor and/or molecular mechanisms mediating the potent anti-inflammatory effects of FAAH substrates in the brain.

References:1 Henry RJ *et al.* J Neuroimmunol (2014) 2 Kerr DM *et al.*, Neuroscience (2012)

Poster Ref: P3-B-035

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Mapping Arc expression in the mouse brain using a novel knockin model.

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Arc/Arg3.1 is an activity-regulated immediate early gene involved in LTP, LTD and homeostatic plasticity. Arc protein is localised specifically to recently-activated synapses where it associates with the scaffold protein complexes assembled by PSD-95[1]. Recent evidence suggests that the subcellular location of Arc affects its role in the synaptic plasticity, with Arc acting at individual synapses to promote local AMPA endocytosis and change spine shape. Arc also localises to the nucleus suppressing cell-wide expression of GluA1 to reduce the strength of all synapses equally[2] (homeostatic plasticity).

In order to understand the relationship between Arc and other PSD proteins *in vivo* we have generated a knock-in mouse line where the endogenous Arc protein is tagged by the Venus fluorescent protein. This mouse model has enabled us to visualise accumulations of Arc protein at individual synapses and nuclei, and to map these across whole brain sections. Stimulation with kainic acid and ketamine drive expression of Arc with distinct temporal and spatial distributions. Crossing the Arc-Venus mice with mice lacking postsynaptic scaffold proteins shows alterations in Arc synaptic expression. This finding is particularly interesting given the enrichment of disruptive mutations in the components of Arc, PSD95 and PSD93 complexes in schizophrenia[3,4].

1. Fernandez *et al.* 2009, Molecular Systems Biology, 5:269
2. Korb *et al.* 2013, Nature Neuroscience, 16(7):874-83
3. Kirov *et al.* 2012 Mol Psychiatry, 17:142-153
4. Purcell *et al.* 2014, Nature, 506:185-190

Poster Ref: P3-B-036

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Interactions of astrocytic ionic fluxes and physiological functions.

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The University of Warwick

Brain function rests on the interaction of two distinct populations of cells: neuronal network and electrically non-excitable glial cells. Astrocytes' functions include both the modulation of excitability of neighbouring neurons and keeping homeostatic balance of the brain, in particularly the potassium and pH homeostasis. Our work has focused on the connection between ionic channels of astrocytes and physiological function of regulating extracellular concentrations of ions. Whole-cell potassium currents were recorded in the acutely isolated astrocytes of somatosensory cortex layer II/III. The modulation of potassium currents by other ionic channels, such as P2X and NMDARs receptors was investigated; activation of these receptors (by [10] μM αβme-ATP and [30] μM NMDA) causes a potentiation of potassium current by 30 and 37% respectively. This mechanism was found to be calcium-dependent, as no effect was seen in experiments with intracellular 10 μM EGTA; potassium currents responsible for this effect were found to be 4-AP sensitive. Thus, the external neuro- and gliotransmitters can influence the activity of voltage-gated potassium channels and through those, the process of the removal of excess K+ from extracellular space (''K+ siphoning''). The effect of modulating ionic fluxes on potassium buffering and in turn on control of tissue volume and osmolarity is explored. Potassium currents across 4 age groups (spanning from 1 to 24 months) are also compared to see if this mechanism alters with age. The data contributes to the current understanding of the molecular processes linking signalling and physiological functions of astrocytes.

Poster Ref: P3-B-037

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Umami taste signalling in hypothalamic tanycytes.

Greta Lazutkaite and Nicholas Dale

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Hypothalamic tanycytes are glial cells that line the wall of the 3rd ventricle and send processes into the brain parenchyma. Among other functions such as thyroid hormone metabolism and the control of blood-hypothalamus barrier permeability, they may help to inform the arcuate nucleus and ventromedial hypothalamus about nutrient availability in the cerebrospinal fluid. We have recently shown that tanycytes sense glucose *via* the sweet taste receptor (a T1R2/T1R3 heterodimer) originally described in the taste buds of the tongue. A receptor for another taste modality – umami – is part of the same gene family as the sweet taste receptor and comprises of a T1R1/T1R3 heterodimer. We have therefore studied whether tanycytes might be able to detect amino acids *via* the umami taste receptor.

We used Fura-2 imaging of intracellular Ca^{2+} to assess the responses of tanycytes in acutely prepared rat brain slices to L-amino acids – arginine, lysine, alanine, serine and proline. Tanycytes responded to all of these agonists in order of potency (Arg>Lys>Ser>Ala>Pro). We found that the responses to these amino acids could be enhanced by prior application of IMP, a known allosteric modulator of the T1R1/T1R3 receptor.

Tanycyte responses to amino acids required extracellular Ca^{2+} and were blocked if the internal stores of Ca^{2+} were depleted by cyclopiazonic acid. The responses to amino acids were also strongly reduced in presence of a combination of a selective P2Y1 receptor antagonist (MRS2500) and a non-selective P2 antagonist (PPADS), suggesting that ATP release and detection were crucial parts of the tanycyte amino acid signalling pathway. Neither antagonist was effective on its own. The ATP release appeared to come *via* connexin hemichannels as it was blocked by high doses of carbenoxolone (100 μM) and the connexin 43 mimetic peptide GAP26, but only weakly affected by relatively selective pannexin blockers probenecid and 10 μM carbexolone.

Our results show the first non-neuronal mechanism for amino acid detection and the first example of signalling *via* the umami taste receptor in the mammalian brain. Full understanding of the amino acid sensitivity of tanycytes may help to devise new strategies for countering the rising tide of excessive weight gain and obesity.

Poster Ref: P3-B-038

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Proteomic profiling of cranial (superior) cervical ganglia reveals beta-amyloid & ubiquitin proteasome system perturbations in an equine multiple system neuropathy.

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Equine grass sickness (EGS) is an acute, predominantly fatal, multiple system neuropathy of grazing horses. The precise aetiology remains unclear, but it likely results from the ingestion of an unidentified neurotoxin. Ultrastructural findings suggest that the primary lesion is in the glycoprotein biosynthetic pathway of specific populations of neurons. The goal of this study was to identify the molecular processes underpinning neurodegeneration in EGS by incorporating an isobaric tag for a relative and absolute quantitation based comparison of the proteome of the cranial (superior) cervical ganglion (CCG – a consistently affected tissue) from EGS and control horses. Our study has identified 2311 unique proteins in CCG extracts, with 320 proteins increased and 186 decreased by greater than 20% relative to controls. Further examination of selected proteomic candidates by quantitative fluorescent western blotting (QFWB) and sub-cellular expression profiling by immunohistochemistry, highlighted a dysregulation in proteins commonly associated with cell stress and protein misfolding/aggregation responses, including but not limited to amyloid precursor protein (APP) and multiple components of the ubiquitin proteasome system (UPS). No plausible causal bacterial or fungal proteins were identified in CCG from EGS horses. Differentially expressed proteins eligible for in silico pathway analysis clustered predominantly into the following biofunctions: 1. Diseases & disorders including; neurological disease, skeletal & muscular disorders; 2. Molecular and cellular functions: including cellular assembly & organisation, cell-to-cell signalling and interaction (including epinephrine, dopamine & adrenergic signalling and receptor function) and small molecule biochemistry. Interestingly, whilst these biofunctions may represent pathways underpinning EGS induced neurodegeneration, they also suggest a degree of conservation with the molecular processes described in many human neurodegenerative conditions. In summary, the experiments detailed here advance our understanding of the molecular processes occurring in this multiple system neuropathy and implicate previously unreported dysregulation of the UPS and APP in EGS neurodegenerative processes.

Poster Ref: P3-B-039

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Reactive oxygen species, metabolic by-products of mitochondrial respiration, are regulators of synapse growth and structural homeostasis.

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Neurons exhibit extensive developmental and homeostatic plasticity. Adjustments in connectivity, excitability and morphology within individual neurons and neuronal networks conspire to maintain a pre-determined activity set-point, in order to remain within a physiologically appropriate range of function. We reveal a novel and fundamental mechanism by which neurons monitor their activity state, a process necessary and sufficient for structural homeostatic adjustment. Maintenance of membrane polarisation, especially in highly active neurons, is extremely energetically demanding, placing a high burden upon the mitochondrial network. Mitochondria constitutively produce Reactive Oxygen Species (ROS) as a by-product of ATP production due to electron leakage from mitochondrial complexes I and III.

Our data reveal that ROS act as second messengers, monitored by cells as a proxy for neuronal activity and capable of driving structural homeostatic adjustments of synaptic terminals. In this context, ROS signalling appears to centre around hydrogen peroxide (H2O2) and its interaction with a putative ROS-sensor, Parkinson's disease-linked, DJ-1b. DJ-1b, in a redox sensitive manner, interacts with and inhibits the lipid phosphatase PTEN. In doing so DJ-1b – PTEN interactions release inhibition of PI3K-signalling, a potent pro-growth signal and a known regulator of neuronal morphology.

Until recently, ROS were considered a tolerated burden, rapidly and naively removed by the cell. However, this and other recent studies, reveal an important role for ROS signalling during normal neuronal function. Our data show that neurons use ROS as second messengers to measure levels of neuronal activity, a process essential for homeostatic adjustment.

Poster Ref: P3-B-040

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Withdrawn

Poster Ref: P3-B-041

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Chondroitin sulfate proteoglycan distribution after acute optic nerve injury.

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Retinal ganglion cells (RGCs) carry visual information from the retina to the brain *via* their axons. Like other central nervous system (CNS) neurons, RGC axons have limited ability to regenerate once injured or damaged by disease. Stimulating regeneration through the optic pathway could provide treatment for vision loss due to trauma or blinding conditions such as glaucoma. Successful regeneration requires an adequate stimulus to initiate regrowth of RGC axons, as well as a means of overcoming the growth-inhibitory environment of the adult visual system. Regenerating RGC axons must retrace a complex path that takes them out of the eye, along the optic nerve, through the optic chiasm, and into the optic tract and the brain. During development, specific guidance cues are expressed in a tightly regulated temporal and spatial manner to create a pro-migratory environment for newly projecting RGC axons. Absence of these cues in the adult optic pathway may account for the observed misguidance of regenerating RGC axons. Furthermore, extracellular proteins such as chondroitin sulfate proteoglycans (CSPGs) are known to accumulate after injury and may contribute to a growth-inhibitory microenvironment in the optic nerve. In this pilot study, we examined the distribution of CSPGs in the murine optic pathway after acute injury. Unilateral optic nerve crush surgery was performed, and tissue was observed at 1, 3, 7, and 14 days after injury. Frozen sections were obtained and stained for CSPGs and glial cells using CS56 and GFAP antibodies, respectively. CSPG upregulation was seen proximal to the injury site at multiple time points and corresponded with a GFAP-negative zone. This evidence reaffirms that CSPGs play an integral role in the injury response, and provides a key framework for future studies that will investigate post-translational modifications to CSPGs including patterns of sulphation, which may more precisely regulate their inhibitory role.

Poster Ref: P3-B-042

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Visual word recognition: functional connectivity using Granger causation analysis in EMEG source space.

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A neurobiological theory of visual word recognition will need to both specify the major brain regions that support this important component of skilled reading, and to map out the timing and the manner in which these regions contribute to word identification and meaning extraction. This in turn requires an analysis of the dynamic functional connectivity between these brain regions over time.

To achieve this we used Granger Causal Modelling [1] applied to source localised MR-constrained combined MEG and EEG (EMEG) data [3] with 1 ms temporal resolution and up to 5 mm spatial resolution. An activation-based bottom-up approach was used to extract regions of interest for the functional connectivity analyses using the Granger Processing Stream (GPS) Toolbox. This employs a Kalman Filter approach to overcome stationarity problems in time series analysis [2].

We applied GPS to two different sets of 150-200 written words, varying in their linguistic complexity (simple *vs* morphologically complex: *e.g.* biscuit *vs* jumped) and focused on the later lexical analysis processes triggered by these words over a 300-450 ms time window (from stimulus onset).

These preliminary analyses reveal major processing hubs defined by their functional connectivity. For complex words these hubs included L-SMG, L-Pars Orbitalis, R-AG and R-Fusiform areas. For simple words major hubs included L-STG, R-ITG and R-AG. In current work we are exploring the computational implication of these functional connections.

References

1. Gow, D.W., & Caplan, D. (2012). New levels of language processing complexity and organization revealed by Granger causation. Frontiers in Psychology, 3, 506. doi: 10.3389/fpsyg.2012.00506

2. Milde, T., Leistritz, L., Astolfi, I., Miltner, W.H.G., Weiss, T., Babiloni, F., & Witte, H. (2010). A new Kalman filter approach for the estimation of high-dimensional time variant multivariate AR models and its application in analysis of laser-evoked brain potentials. NeuroImage, 50, 960-969. Doi: 10.1016/j_neuroimage_2009.12.110.

3. Whiting, C.M., Shtyrov, Y., & Marslen-Wilson, W.D. (2014). Real-time functional architecture of visual word recognition. Journal of Cognitive Neuroscience.

Poster Ref: P3-B-043

Theme: B: Molecular, Cellular and Synaptic Mechanisms

Investigation of oscillations in the avian hippocampus.

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Introduction: Gamma rhythms are a physiological feature of the mammalian hippocampus and play an important role in memory processing. However, such oscillations have not been explored in the avian hippocampal formation (HF) whose neuroanatomy is unlike its mammalian counterpart. We therefore investigate how divergent structures perform convergent functions. If similar micro-circuitry underlies the avian HF, then we would predict that similar network properties should be detectable.

Aims: We investigate the existence of gamma oscillations in avian HF, the underlying mechanisms of rhythmogenesis and the role of different receptors in this activity.

Methods: We euthanized newly hatched chicks by cervical dislocation. We employed *in vitro* electrophysiology to record local field potentials in chick brain slices (400 µm). Bath application of various agonists and antagonists allowed us to elucidate the receptor pharmacology of avian hippocampal gamma oscillations *in vitro*.

Results: In P0 - P4 chick HF brain slices, persistent gamma frequency oscillations (peak power: 64 ± 24.8 µV2/Hz; peak frequency: 36 ± 1.4 Hz; n = 27 slices) were induced by the bath application of the cholinergic agonist, carbachol (10 µM). However, the bath application of kainate (50 - 800 nM), a glutamate receptor agonist, did not elicit gamma. Similar to other species, carbachol-evoked gamma oscillations were sensitive to GABA-A, AMPA/kainate and muscarinic (M1) receptor antagonism.

Conclusions: We conclude that in juvenile chick HF, gamma rhythmogenesis is cholinergic in nature. This is unlike in adult mammals where both cholinergic and glutamatergic mechanisms are known to exist. However, similar to mammalian species, muscarinic acetylcholine receptor (mAChR) activated avian HF gamma oscillations are likely to arise via a pyramidal-interneuron gamma (PING) based mechanism.

Theme C: Sensory and Motor Systems

Posters P3-C-001 to P3-C-030

Poster Ref: P3-C-001

Theme: C: Sensory and Motor Systems

Changes in whisking behaviour during object exploration in "cortically-altered" mice.

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Rodents rhythmically sweep their whiskers back and forwards in a behaviour termed ‘whisking’. During surface exploration, rodents employ active control strategies, which increases the information acquired from an object. The emergence of these behaviours in neonates coincides with the development of upstream cortical regions; however, limited studies have specifically examined the role of the cortex in active vibrissal sensing. This study examines the effect of cortical alterations on exploratory whisker behaviours in three different transgenic mice: Barreless, RIM-DKO-sert and Krox20::Cre;Robo3lox/lox. Vibrissae movements were tracked in video recordings during contact and non-contact episodes and whisker kinematics were measured including: frequency, amplitude, asymmetry, retraction, offset and spread. Only RIM-DKO-sert mice showed a change in exploratory behaviour during active touch exploration; they were unable to reduce their whisker spread and regularly froze following an initial whisker contact. These findings suggest that the cortical regions of the brain are involved in whisking behaviours during object exploration, and, in particular, the thalamocortical circuits effect inquisitive, exploratory whisker movements.

Poster Ref: P3-C-002

Theme: C: Sensory and Motor Systems

Whisker velocities are affected during smoking: insights in to motor control.

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Active whisking in mice and rats is one of the fastest behaviours known to mammals and is characterised by a range of complex behaviours, including alterations in whisker timings, speeds and positions. The neuronal structures that are associated with these complex behaviours are arranged in a network of parallel, nested sensorimotor loops, but how these networks might control such a broad range of whisking behaviours is not yet known. This study aims to explore the effect of nicotine on whisking in mice, to reveal insights in to the role acetylcholine may play in the whisker system. We compare here the whisking behaviour of non-smoking and smoking mice, that have been exposed to a nose-only cigarette system for 3 months, and also mice that have stopped smoking for one and two weeks. We show that whisker amplitudes and velocities work together to maintain whisk frequency, and that breathing and whisking de-couple in the smoking animals. We find that both protraction and retraction whisker velocities are significantly increased in smoking mice, and suggest that nicotine interacts with associated brain structures to give rise to these changes. We suggest that whisker velocity might demonstrate exploratory intent, where slower phases of the whisk cycle correspond to areas of interest. Whisker velocities, therefore, might indicate exploratory intent and attention, and shows support for acetylcholine being involved in awareness, attention and alertness pathways.

Poster Ref: P3-C-003

Theme: C: Sensory and Motor Systems

Olfactory ensheathing cell transplants improve vertical climbing in rats after cervical level dorsal root rhizotomy.

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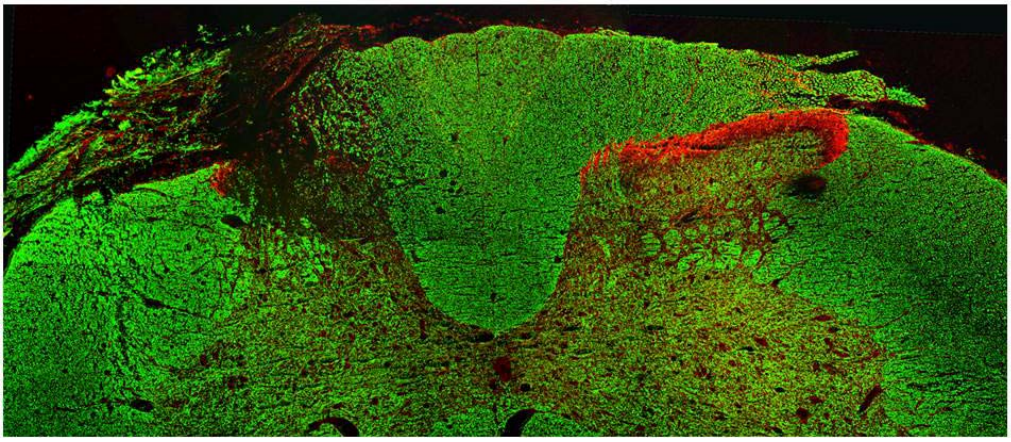
A brachial plexus injury (BPI) involves damage to spinal roots at the cervical level of the spinal cord. Such injuries most often result from road traffic accidents and can lead to sensory or motor impairment. Up to 90% of BPI patients also face permanent pain, described by some as a “burning and crushing” sensation on their arm. A lack of relevant preclinical models is one factor behind the lack of effective treatments.

Transplants of olfactory ensheathing cells (OECs) have evoked long distance axon regeneration in thoracic level lesions and restored breathing in a high cervical injury model. A matrix method of transplantation was developed to ensure retention of the OEC transplant at the dorsal root entry zone. We sought to establish a rat model of dorsal root injury (DRI) which mimics both the sensory impairment and pain aspect of a BPI. The effect of OEC transplants on these parameters would then be assessed.

Unilateral transection of C6, C7, C8 and T1 dorsal roots at the dorsal root entry zone (DREZ) led to a long-term forelimb sensory deficit. Proprioceptive function and forepaw tactile sensitivity were measured using vertical cage climbing and adhesive tape tests, respectively. Those rats which received an acute transplant of GFP-labelled OECs climbed better than controls, despite maintaining a deficit in forepaw tactile sensitivity.

Immunohistochemical staining of the DREZ and dorsal horn revealed histological differences between ipsilateral and contralateral sides after C6-T1 rhizotomy. Markers for GFAP, laminin, CGRP, neurofilament and VGLUT were identified on transverse and longitudinal sections at various time points up to 8 weeks post-injury. Clear differences were apparent between intact and injured regions but further quantitative analysis is required to determine any potential effect of OECs.

A C7C8 dorsal root avulsion study is ongoing which is more likely to induce forepaw sensitivity to cold, mechanical or thermal stimuli due to greater vascular damage and cell loss at the dorsal horn. Specific preclinical models of cervical injury tailored to study either sensory impairment or pain should allow us to assess the efficacy of OECs and optimize their use in patients.



The extent of rhizotomy-induced damage within the superficial dorsal horn of the rat cervical spinal cord. Small diameter peptidergic fibres (CGRP; red) and neurofilament-stained axons (green) allow comparison of ipsi- and contralateral sides to the injury.

Poster Ref: P3-C-004

Theme: C: Sensory and Motor Systems

Investigation of functional domains in acid sensing ion channels (ASICs) through characterisation of chimeras.

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The acid-sensing ion channels (ASICs) are a family of ion channels expressed throughout the mammalian nervous system. The principal activator of ASICs is extracellular protons and ASICs have been demonstrated to play a significant role in many physiological and pathophysiological processes including synaptic transmission, nociception and fear. However, not all ASICs are proton-sensitive: ASIC2a is activated by acid, whereas its splice variant ASIC2b is not. We made a series of chimeric ASIC2 proteins and using whole-cell electrophysiology we have identified the minimal region of the ASIC2a extracellular domain that is required for ASIC2 proton-activation: the first 87 amino acids after transmembrane domain 1. We next examined the function of different domains within the ASIC2b N-terminus and identified a region proximal to the first transmembrane domain that confers tachyphylaxis upon ASIC2a. We have thus identified domains of ASIC2 that are crucial to channel function and may be important for the function of other members of the ASIC family.

Poster Ref: P3-C-005

Theme: C: Sensory and Motor Systems

Resting state functional connectivity of primary visual cortex under LSD.

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Lysergic acid diethylamide (LSD) is a hallucinogen and classic psychedelic drug. The altered state of consciousness produced by LSD is characterized by visual hallucinations. In the present analysis, we measured changes in resting-state functional connectivity (RSFC) between the primary visual cortex (V1) and the rest of the brain under the influence of LSD in a balanced order, within-subjects, placebo-controlled design. Twenty healthy subjects received 75 micrograms of LSD and separately saline (placebo) *via* intravenous infusion. Five subjects were discarded from the analysis due to high level of head movement. Subjects had two 7 minutes fMRI (BOLD) scans (eyes-closed 'resting-state') in each condition. LSD produced marked changes in V1-RSFC. Specifically, increased RSFC was observed between V1 and the bilateral striatum, insular cortex, operculum cortex, orbitofrontal cortex, inferior frontal gyrus, superior and middle temporal gyrus, supramarginal gyrus, angular gyrus, paracingulate gyrus and medial posterior thalamus. There were no decreases in V1-RSFC under LSD. Since V1 is centrally involved in visual processing, these results suggest that increased communication between V1 and several brain regions may underlie LSD's characteristic effects on visual perception. Further analyses will be performed to investigate altered visual system function under LSD and its relationship to visual hallucinations. These results may have implications for the neurobiology of visual hallucinations and visual processing more generally. This was the first modern neuroimaging study with LSD. That the drug produced robust effects and was well tolerated by the participants augurs well for future LSD research.

Poster Ref: P3-C-006

Theme: C: Sensory and Motor Systems

Recovery of overground locomotor function with epidural stimulation, treadmill training and chondroitinase ABC following severe contusion injury

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Electrical epidural stimulation (ES) of the lumbar spinal cord (L2 to S1) has previously been shown to improve locomotor function in complete transection models of rat spinal cord injury (SCI) in conjunction with monoaminergic and serotonergic agonists and bipedal locomotor training. However, this functional improvement does not translate into recovery of overground locomotion and previous evidence has shown that rehabilitation up-regulates inhibitory chondroitin sulphate proteoglycans in the lumbar spinal cord therefore restricting synaptic plasticity. It was therefore our premise for this study that addition of lentiviral chondroitinase (LV-Chase) locally after injury would enhance plasticity thus allowing for enhanced functional recovery. Adult Sprague-Dawley rats received a severe spinal contusion injury (T9/10), epidural implantation at segmental levels L2 and S1 and intra-spinal injections of LV-Chase or saline (control). Rats were then randomly assigned to one of four groups: cage control, training only, ES only (40 Hz; L2) or ES+training. Rats in either trained group stepped bipedally on a body weight supported treadmill (5-16 cm/s) (5 days/week, 20 mins/day) for 8 weeks. By the end of the 8-week period rats in the Saline+ES+training group showed improvements not only in supported treadmill stepping ability but also in open field locomotion (BBB), with combination saline/LV-Chase treated animals achieving the highest overall increase in mean BBB score compared to Saline/LV-Chase controls. We did not observe any electromyography responses of hindlimb muscles following cortical stimulation in any animal from any group, and no increased sensitivity to mechanical pain stimulation. Therefore these results suggest that a combination of step training and epidural stimulation in an incomplete model of SCI successfully improved locomotor function further than either therapy administered alone regardless of intraspinal application of LV-Chase. Combination treatment animals not only improved in treadmill step performance but were also able to transfer this skill to an open field task, with such improvements being independent of corticospinal modulation.

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Poster Ref: P3-C-007

Theme: C: Sensory and Motor Systems

Spatial summation reveals frequency- and layer-specific pattern of LFP oscillations in primate V1.

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Neurons of primary visual cortex (V1) typically show a lower response to visual stimuli when the stimuli are covering the neurons' receptive field (RF) as well as areas of the visual field surrounding the RF (surround suppression). We have shown earlier (Gieselmann and Thiele, 2008) that simultaneous to the decrease in firing rate, the local field potential (LFP) recorded from the same electrode shows an increase in oscillatory activity in the gamma range, as stimuli extend into the inhibitory surround. To identify to what extent these effects differ between cortical layers and to identify the networks involved in the generation of gamma oscillations we used multi-contact laminar recordings of the LFP and current-source density analysis (CSD).

We recorded from 16-channel laminar electrodes inserted perpendicularly into the primary visual cortex. Electrode contacts were arranged vertically along the probe with a distance of 150 µm between them. We trained two awake monkeys on a passive fixation task during which they were presented with a series of square-wave gratings of different sizes. We analysed 24 experiments (17 in monkey, 7 in monkey 2). For all experiments recording channels were aligned in depth to an early potential reversal corresponding to layer 4c. We then calculated the LFP signal generated locally at each channel by estimating the CSD on a trial-by-trial basis.

While large grating stimuli (>7° diameter) consistently induced strong sustained gamma oscillations around 40 Hz they reduced oscillatory power in frequencies <20 Hz and >60 Hz. These modulations were specific to four laminar compartments. Reductions in LFP power were mainly observed in the supra- (2/3) and infra-granular (5/6) layers. The increase in LFP gamma power peaked in upper-granular (4a/4b) and infra-granular layers and was lowest in lower-granular (4c) layers. Interestingly, while the coherence of oscillations between these laminar compartments was also modulated by stimulus size we found strong coherence in low frequencies (8-20 Hz) between supra- and infra-granular layers that was not affected by stimulus size. Thus, spatial summation and surround suppression do manifest in columnar circuits that are laminar-specific and which interact in a frequency-specific manner.

Poster Ref: P3-C-008

Theme: C: Sensory and Motor Systems

Glutamatergic control of attentional signals in macaque frontal eye-field.

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Attention improves perception by affecting different aspects of the neuronal code. It enhances firing rates, it reduces firing rate variability and noise correlations of neurons, and it alters the strength of oscillatory activity. In striate cortex, attention induced rate enhancement requires cholinergic mechanisms(1), while attention induced variance and noise correlation reduction are supported by (glutamatergic) NMDA receptor availability(2). Here we investigate how glutamate affects attentional signals in the frontal eye-field (FEF). Two male macaque monkeys were trained in a covert top-down attention task, where a central colour cue indicated on a trail by trial basis where to attend to. The animals had to detect a change of the cued stimulus and ignore changes in un-cued stimuli. They responded by releasing a touch bar to obtain a fluid reward. 90 cells where tested with AMPA/Kainate receptor antagonist and 134 cells with NMDA receptor antagonist. Attention to the neuron's receptive/movement field significantly increased firing rates ($p<0.05$). Both NMDA and AMPA/Kainate receptor blockade reduced the spike rate. NMDA receptor blockade did not affect attentional rate modulation (assessed by means of ROC and attentional modulation index). But AMPA/Kainate receptor blockade reduced the attentional rate modulation ($p<0.05$). NMDA receptors in FEF seem to have a very different role compared to V1 where NMDA receptor blockade reduces ROC(2). And the opposite is found with AMPA/Kainate receptor blockade where we found a reduced attentional rate modulation compared to no significant effect in V1. Thus, area, and function specific involvement of neurotransmitters and associated receptors are an important feature of the cortical architecture.

Supported by the Wellcome Trust.

1.Herrero JL, *et al.* (2008) Acetylcholine contributes through muscarinic receptors to attentional modulation in V1. Nature 454(7208):1110-1114.

2.Herrero JL, Gieselmann MA, Sanayei M, & Thiele A (2013) Attention-induced variance and noise correlation reduction in macaque V1 is mediated by NMDA receptors. Neuron 78(4):729-739.

Poster Ref: P3-C-009

Theme: C: Sensory and Motor Systems

Using a mobile EEG system for neurofeedback training to enhance hemispheric lateralization in motor execution.

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Introduction: Poor motor recovery in stroke is associated with a more bilateral pattern of brain activation. In patients with better functional outcomes, activation tends to become more lateralized, paralleling their recovery process. Thus, a potential neuro-rehabilitation strategy is to lateralize brain activity with neurofeedback. As an initial step for developing a bedside intervention tool for stroke, the current study investigates the use of a low-cost, mobile EEG system for neurofeedback in promoting hemispheric lateralization in healthy volunteers.

Methods: In a within-subjects design, participants underwent both real and sham neurofeedback conditions (single-blind, counterbalanced); each consisted of four training sessions that took place on different days. The participants performed finger tapping movements while attempting to modulate the feedback. In the real condition, feedback was derived from online analysis and classification of EEG mu (8-13 Hz) and beta (13-25 Hz) activities with common spatial pattern filter and support vector machine algorithms during finger tapping. In the sham condition, a video playback of the feedback from another participant was used. EEG data were acquired with a modified wireless Emotiv Epoc amplifier, with electrodes covering bilateral motor cortices. Event-related de-synchronization (ERD) was computed as a measure of lateralization, and resting-state MRI scans were also conducted before and after each set of training to examine changes in functional connectivity with neurofeedback training.

Results and Conclusions: Classification accuracy improved with real feedback training but not in the sham condition. In addition, lateralized ERD only increased with real neurofeedback training, indicating that there was an increased in laterality during motor execution. Furthermore, resting state analysis revealed stronger functional connections between premotor areas and motor network after real feedback training. This is consistent with the hypothesis that EEG motor rhythms may have arisen from the downstream modulation of motor neurons from the premotor cortex. These findings provide evidence that neurofeedback with a mobile EEG system can increase hemispheric lateralization and alter functional connectivity of the motor areas.

Poster Ref: P3-C-010

Theme: C: Sensory and Motor Systems

Specificity of the murine cortico-tectal connectivity and its possible role in orienting and attention based behaviour.

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Background: Action planning is context dependent and requires processing of sensory information, decision making and motor output generation. These complex operations require the interaction of many cortical and subcortical areas. An important subcortical structure in this process is the Superior Colliculus (SC), which aids orienting behaviours and plays an important role in attention. Recent research in the rat suggests that different parts of the SC are involved in avoidance vs. approach behaviours, whereby these different subzones were segregated in terms of their cortical connectivity.

Objectives: Delineate the cortico-tectal connectivity profiles of the lateral and medial superior colliculus (SCl and SCm) in the mouse and relate these to their potential role in goal directed behaviour.

Methods: We iontophoretically injected Fluorogold (FG), a retrograde tracer, into the lateral or medial murine SC. After a three day survival time, the animals underwent cardiac perfusion with a fixative. The tissue was frozen and cryosectioned at 40 microns. Analysis of connectivity was performed by mapping retrogradely labelled cells in the cortex onto representative atlas slides. Mapping of the retrogradely transported FG was visualised by fluorescent microscopy.

Results/Discussion: Cortical and subcortical input to then SC differed for the medial and lateral subsections, even if some overlap was found. To highlight a few example differences, the body and limb rperesenations of the somatosensory cortex projected predominatly to the SCm, while barrel cortex and facial representations mostly terminated in SCl. The SCm was connected to auditory cortical areas such as Au1, AuD whereas the SCl was not. The SCm received more input from the Cingulate cortex (CC) when compared to SCl. In addition there seemed to be a different in laminar depth, with SCm projections arising from Layer 3 and SCl projections arising from Layer 5 of CC. Finally, the SCl received more input from frontal motor regions M2 and M1.

Conclusion: The results suggest that the murine SC is subdivided into components that support either approach or avoidance behaviour. It also suggests that different subzones of the SC are differently involved in attention and orientating.

Supported by MRC.

Poster Ref: P3-C-011

Theme: C: Sensory and Motor Systems

Mechanosensory pathways as potential targets for the control of insect-borne diseases.

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Vector-borne infectious diseases, especially those spread by mosquito species, include some of the major plagues of humanity and annually cause millions of deaths worldwide. Transmission of these diseases is inextricably linked to the biology of mosquitoes.

Our studies investigate the mechanosensory bases of various aspects of mosquito behaviour. For example, it seems very likely that, in order to insert their proboscis into the human skin, mosquitoes rely on sensory feedback from mechanosensory organs, such as *e.g.* chordotonal organs. We test this by ablating chordotonal organ function using chordotonal-specific insecticides.

Mechanosensory, and specifically chordotonal, signalling, however, is also a crucial component of the animals' air-borne courtship, and copulatory, behaviour. The same strategy that impairs the animals' ability to insert their probosces into human skin could thus also directly impact the animals' reproduction rate. Using *Drosophila melanogaster* as a model organism, we have tested the potential impact of ablating chordotonal organ on different parts of the reproductive cycle – in particular the male courtship song and the relative fecundity of females.

In addition to this, mosquito biting habits have a strong circadian component, with biting only occurring during specific parts of the day. Any impairment of clock function could therefore significantly change the biting frequency of the insect. We examined the circadian rhythm activity patterns (in response to stimulation using light or temperature) of *Drosophila* with ablated chordotonal organ function in order to explore any alterations in behaviour patterns.

Results and implications of these experiments will be analysed with newly devised computational models of disease transmission, using the degree of mechanosensory impairment as a novel model parameter.

We anticipate that our approach will lead the way to new strategies of vector control.

Poster Ref: P3-C-012

Theme: C: Sensory and Motor Systems

Anatomical connectivity of temporal voice areas.

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Temporal Voice Areas (TVAs) are cortical regions located along the superior temporal sulcus, which show greater activation for vocal than non-vocal sounds. Importantly, this is the case regardless of whether the stimuli contain speech (Latinus & Belin, 2011). They were found to be present in 4-7 months old infants, and observed in others species, namely monkeys and dogs, suggesting an early appearance of TVAs in human development and evolution (Andics *et al.*, 2014; Latinus & Belin, 2011; Bestelmeyer, Belin, & Grosbras, 2011; Perrodin *et al.*, 2011; Belin & Grosbras, 2010). Research with postlingually deaf individuals and native signers shows that TVAs are assigned to process sign language and/or speech reading during deafness, but process voices in hearing native signers and individuals with cochlear implants (MacSweeney *et al.*, 2006; Rouger *et al.*, 2012), supporting the notion of voice rather than speech selectivity. Taken together, the evidence suggests that the TVAs constitute a crucial stage in voice cognition abilities in the cerebral network (Bestelmeyer, Belin, & Grosbras, 2011).

The TVAs are organised in three clusters (Belin, Zatorre, Lafaille, Ahad, & Pike, 2000) and the present project aims to establish the anatomical connectivity of these clusters, both locally and globally. Seventy participants received an fMRI 'voice localizer' and diffusion MRI scan, allowing for a functional and structural investigation at the single-subject and group level using seed based probabilistic tractography. Preliminary results suggest greater long range connectivity of the posterior cluster to the frontal lobe compared to the anterior and mid-TVAs as shown in Figure 1. Given that the exact location of TVAs varies between individuals, single subject analyses will be carried out to establish the full extent of differences in anatomical connectivity.

References

Andics *et al.*, (2014). Current Biology, 24

Bestelmeyer, Belin, & Grosbras (2011). Current Biology, 21(20)

Belin, & Grosbras (2010). Neuron, 65

Belin, Zatorre, Lafaille, Ahad, & Pike (2000). Nature, 403

Latinus & Belin (2011). Current Biology, 21(4)

MacSweeney *et al.* (2006) Human Brain Mapping, 27

Perrodin *et al.*,(2011). Current Biology, 21

Rouger *et al.* (2012). Human Brain Mapping, 33

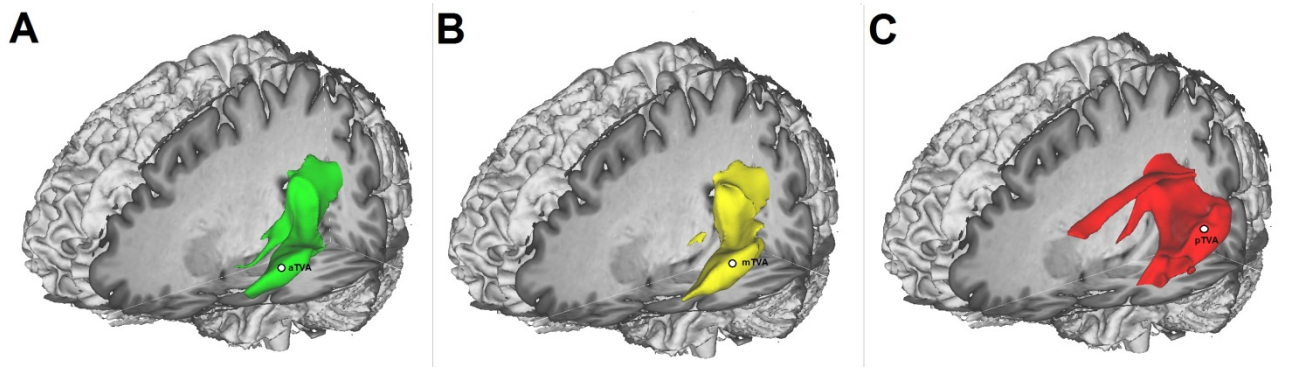

Figure 1. Group connectivity maps for the left hemisphere based on the mean of 70 participants. A) Anterior cluster in green (MNI coordinates: -55, -8, -3); B) mid cluster in yellow (-55, -18, -3); C) posterior cluster in red (-46, -38, 2) displayed with the single subject template anatomy.

Poster Ref: P3-C-013

Theme: C: Sensory and Motor Systems

Parvalbumin-expressing cells are a source of presynaptic (Axo-axonic) inputs on to low threshold hair follicle afferents in the mouse spinal dorsal horn.

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Axo-axonic synapses form the anatomical basis for presynaptic inhibition. These synapses have been described on the central terminals of cutaneous afferents in the spinal dorsal horn, however, the origin of these inputs have yet to be confirmed. We have shown that some presynaptic boutons on myelinated afferent terminals express parvalbumin (PV), and proposed that these were derived from PV cells in laminae IIi and III (Hughes *et al.*, 2012. J. Physiol. 590:3927). Here, we use multiple techniques to verify details of this microcircuit and determine i) the origin of PV-expressing axo-axonic inputs; ii) the origin of the central terminals targeted by inhibitory PV inputs; and iii) the physiological and morphological properties of PV axo-axonic cells.

To determine the sensory modalities served by afferents associated with presynaptic PV inputs, we have used genetic labelling to visualise two classes of low threshold mechanoreceptors (LTMRs) innervating hairy skin (Li *et al.*, 2011. Cell 147:1615). We found anatomical evidence that i) all inhibitory PV-expressing cells in lamina IIi and III receive numerous contacts from Aβ and Aδ LTMRs, and ii) the central terminals of both afferent classes are contacted by inhibitory PV boutons. We have also used a PVcre;tdTOMATO mouse line for targeted patch-clamp recordings from spinal cord slices *in vitro*. We found PV cells i) show tonic firing or initial bursting action potential discharge patterns in response to current injections, ii) show a high prevalence of Ih sub-threshold currents; and iii) receive monosynaptic A-fibre inputs following electrical stimulation of dorsal roots. Subsequent anatomical studies determined that these cells typically show islet cell morphology and that most of their axon targets myelinated afferents.

Our studies demonstrate that PV cells in laminae IIi and III are a source of presynaptic inputs on to the central terminals of hair afferents. We also show that myelinated hair afferents provide an excitatory drive to these cells. While PV cells are likely to be important in the modulation of innocuous tactile sensation, they are also ideally placed to play a central role in the development of central sensitisation and tactile allodynia.

This work was supported by the BBSRC; grant BB/J000620/1

Poster Ref: P3-C-014

Theme: C: Sensory and Motor Systems

Cerebellar calibration of topographic maps in the superior colliculus using the adaptive filter model.

Emma Wilson, Paul Dean, Sean Anderson and John Porrill

University of Sheffield

The intermediate and deep layers of the superior colliculus receive a massive cerebellar input which can directly influence collicular output cells. With the exception of a proposed role in vibrissal noise cancellation, there has been little speculation about the function of this projection. Here we suggest that these cerebellar inputs play a role in calibrating the accuracy of collicular topographic maps.

The adaptive-filter model of the cerebellar microcircuit has been applied to a wide range of sensorimotor skills. Here we investigate whether it can also be applied without change to the very different computational problem of calibrating a topographic map driving an orienting response. We propose a model in which the topographic map constitutes a probabilistic representation of target position obtained from sensory inputs, and the position of peak activity in the topographic map drives the orienting response. The input to the relevant cerebellar microzone is assumed to be a coarse coded representation of the topographic map, while the microzone output shifts the position of peak map activity over a local area of the map (by a process such as attentional gain modulation). Climbing fibre inputs to the microzone carry information about orienting errors, which serves as a teaching signal for cerebellar learning.

We show in simulation that the proposed mechanism can successfully recalibrate topographic maps containing multiple targets which are subject to curvilinear miscalibrations. We also investigate the case of a moving target in which sensory information is delayed relative to target acquisition (as in prey pursuit). The model learns to place targets at their predicted rather than actual positions, producing an accurate and properly timed orienting response.

The model makes firm predictions concerning connectivity, and the signals carried by the component pathways. The proposed mechanism may be applicable to more general neural populations and outputs, greatly increasing the range of tasks for which the adaptive filter model is computationally adequate. This would explain the very wide involvement of the cerebellum not only in sensory and motor tasks, but also in the range of cognitive tasks in which it is increasingly being implicated.

Poster Ref: P3-C-015

Theme: C: Sensory and Motor Systems

Transferring experience of agency from voluntary to involuntary movement: a TMS study.

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Sense of agency refers to the capacity to control one's actions, and, through them, the external world. Internal signals within the basal-ganglia-thalamocortical loops are associated with a conscious sense of trying, or willing. Association between these signals with other events could be a basic mechanism for acquiring sense of agency. This presumably occurs during early human motor development, but is not remembered. We have investigated whether healthy adults could acquire new agency-like experiences with respect to involuntary movements, through such associative mechanisms. We used the perceived temporal relationship between an action and its sensory outcome as an implicit proxy measure of sense of agency.

34 healthy volunteers, 18-35 years of age were tested in two separate experiments. In the first experiment, self-paced voluntary actions of one hand were paired with involuntary twitches of the other hand, triggered by transcranial magnetic stimulation (TMS), followed by a tone 250ms later. These learning trials alternated with test trials containing only involuntary twitches followed by tones. Participants judged the time of the tone using a rotating clock display: a perceptual shift of tone towards preceding action is an established index of agency. In a control experiment, participants again judged the time of the tone following an involuntary twitch, but the twitch was never associated with any voluntary action.

In the first experiment, participants perceived tones as shifted towards the test trials with TMS-induced twitches that caused them. This ‘intentional binding’ was absent in the control experiment.

We showed, for the first time, that coupling an involuntary movement to a voluntary action leads to acquiring an agency-like experience with respect to the voluntary movement. This finding suggests that we learn to be voluntary. This research could guide development of neuroprosthetic systems designed to augment voluntary motor control.

Poster Ref: P3-C-016

Theme: C: Sensory and Motor Systems

Inhibitory input in the mushroom body calyx of larval *Drosophila*.

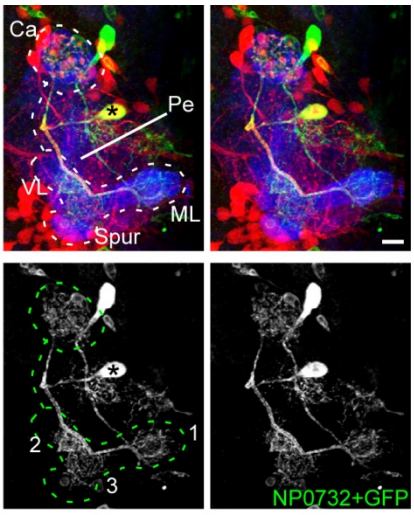
Liria M Masuda-Nakagawa[1], Takeshi Awasaki[2], Kei Ito[2] and Cahir J O'Kane[1]

[1]University of Cambridge, [2]University of Tokyo, Japan

The mushroom bodies of insect brains are higher brain centers essential for associative olfactory learning. The relatively simple *Drosophila* larval mushroom body calyx, the dendritic input region, is organized in about 34 glomeruli, each organized around the terminal of a single projection or other input neuron. We previously found stereotypic innervation of specific calyx glomeruli by projection neuron (PN) terminals, and apparently random innervation by Kenyon cell (KC) dendrites. This pattern of connectivity is consistent with a model in which Kenyon cell dendrites process olfactory input by a combinatorial mechanism that can discriminate a large number of odors.

We generated a sensory map of all 21 sensory neurons in the MB calyx, by defining the pattern of connectivity of individual PNs between specific AL and calyx glomeruli. Using calcium imaging in live larval brains, we showed that stimulation of single OSNs evoked strong neuronal activity in one to three calyx glomeruli, thus showing some limited divergence of odor representations in the transition from OSNs to calyx glomeruli.

However, the specificity of odor representations in the calyx is subject to modulation. We have therefore screened a GAL4 collection and identified a number of lines that label non-PN non-KC neurons that innervate the calyx. One line labels a neuron that innervates the MB calyx and lobes. This neuron is similar in morphology to the adult APL, and we therefore designate it as the larval APL. Terminals in the calyx are GABAergic and presynaptic, and processes in the lobes express DenMark but not presynaptic markers and therefore appear dendritic. GRASP between KCs and the larval APL neuron shows proximity of their processes in the calyx. The larval APL responds to odors, and inhibition of synaptic output from MB neurons by shibire[ts] decreases larval APL activity. The larval APL is the single inhibitory input to the calyx and functions as a feedback neuron connecting MB output to the calyx. Additional novel lines innervate calyx glomeruli and their connectivity within the calyx is under investigation.



Frontal stereo view of the larval APL neuron (asterisk), labeled by NP0732-GAL4 expression, and innervating the calyx (Ca) and lobes (VL, ML) of the larval mushroom body (outlined in broken line). Merge colours: NP0732-GAL4, green; Discs large, blue; GABA, red. Scalebar 10 micrometers. From Masuda-Nakagawa et al (2003) Front Neural Circs 8:35,

Poster Ref: P3-C-017

Theme: C: Sensory and Motor Systems

Mechanotransduction in a model stretch receptor.

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Mechanosensation of muscle stretch is essential for proprioception and motor co-ordination. In mammals, it is relayed *via* sensory afferents from muscle spindles. These endings produce a receptor potential in response to stretch that subsequently triggers an action potential train. The molecular basis of the receptor potential is incompletely understood. We have developed an *in vivo Drosophila* model of a defined mechanosensory neuron in the larval body wall that has anatomical similarities to mammalian muscle spindles. Electrophysiological recordings of the receptor potential in these 'dorsal bipolar dendritic' (dbd) neurons can be combined with pharmacological and genetic techniques, to elucidate molecular-level mechanotransduction.

In this model, we demonstrate that dbd neurons show a receptor potential profile in response to stretch that is highly reminiscent of mammalian spindles. Pharmacological analysis suggest that this is largely triggered by a mechanosensory sodium current. RNAi was then used to show that the *Drosophila* homologue of mechanosensory channel Piezo (DmPiezo) is the main contributor to this receptor current. A smaller contribution was also demonstrated for TRPA1.

Whilst the majority of the initial mechanoreceptor current passed by DmPiezo and/or TRPA1 is sodium, some 20% of current is unaccounted for. We are currently testing the hypothesis that this is calcium. In addition, we are exploring the possible role of voltage-gaged Ca channels to aspects of the receptor potential profile. Discovering the current(s) and corresponding channel(s) responsible for the remaining initial depolarisation of the receptor potential, should provide valuable insight into the molecular mechanisms of mechanotransduction, and may provide candidates for analysis in muscle spindles.

Poster Ref: P3-C-018

Theme: C: Sensory and Motor Systems

The reteromeric channels Kv7.2 and Kv7.3 contribute to thermal pain discrimination *via* regulation of the thalamocortical firing pattern.

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Functional Kv7 channels' existence in thalamocortical relay (TC) neurons and impact of M-type K^+-current (IM) on thalamic signal processing have long been debated even if recent evidence suggest their presence in this brain region. Therefore we aimed to investigate their functional role in regulating firing pattern in neurons of the ventrobasal complex of thalamus.

Characterization of these channels was performed by combining *in vitro*, *in vivo* and in silico approaches as following: retigabine and XE991, specific Kv7 channel enhancer and blocker, respectively were applied on acute brain slices for electrophysiological recordings while consequences of intrathalamic injection of retigabine and/or XE991 were investigated in freely behaving animals during hot plate tests paralleled by electrophysiological recordings of thalamocortical neuron activity.

We show that the Kv7.2 and Kv7.3 subunits are abundantly expressed in TC neurons of mouse ventrobasal thalamic complex (VB). A slow K^+-current with properties of IM is shown, activated by retigabine and inhibited by XE991. Kv7-channel activation resulted in membrane hyperpolarization, reduction of tonic action potential firing, and increases in burst-firing *in vitro* and in computational models. A Kv7-mediated increase in pain threshold and was associated with fewer VB units responding to noxious stimuli, and increased burst firing in responsive neurons. Furthermore, the application of retigabine and XE991 did not exert any effect in animals lacking the subunits kv7.2 and Kv7.3.

These findings indicate that IM limits TC neurons' excitability and probably facilitates the LTS-mediated burst firing. Moreover, given the analgesic effect induced by retigabine injection and the known anti-nociceptive effect of thalamic bursting during noxious stimulation, Kv7 channels could be crucial for the gating of sensory modalities offering a new antinociceptive mechanism at the thalamic level.

Poster Ref: P3-C-019

Theme: C: Sensory and Motor Systems

Auditory function, homeostasis and ageing in *Drosophila melanogaster*.

Camille H Tardieu, Liza Malong, Nicholas Boyd-Gibbins, Ryan G Kavlie, Jonathan E Gale and Joerg T Albert
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A crucial, albeit less apparent, component of all sensory organs is the homeostatic machinery that maintains their functionality across the life span.

Here we use the fruit fly *Drosophila* to study the homeostasis of hearing with a specific emphasis on the homeostasis of the core machinery responsible for converting sound into neuronal excitation, *i.e.* the auditory transducer complex. Auditory homeostasis is assessed at molecular, anatomical, biophysical and electrophysiological system levels .

Preliminary analysis of auditory mechanics together with extracellular nerve recordings suggest that there are both biomechanical and electrophysiological changes in the fly ear throughout ageing. Functional recovery experiments, however, which used adult-specific de novo synthesis of NompC channel proteins in a nompC null mutant background found both biomechanical and electrophysiological recovery of auditory transduction. This suggests a significant homeostatic regulation of core components of the fly's auditory transducer machinery.

We therefore assayed the turnover of key mechanotransducer molecules. To study the possible proteostasis of a core component of the fly's auditory transducer apparatus, the TRP channel NompC(=TRPN1), Fluorescence Recovery After Photobleaching (FRAP) experiments were performed in live animals. FRAP analysis demonstrated a virtually complete turnover of NompC molecules within ~24 hours, involving the translocalization of new channel proteins to the transducer sites in the distal cilium.

A breakdown of transducer proteostasis could thus be a possible cause for the functional auditory decline during ageing. In order to provide a more complete understanding of how ageing alters protein expression in the auditory organ, we use high-throughput RNA-sequencing combined with complementary quantitative real time PCR (qPCR) and bioinformatical analyses. The initial results from these experiments will be presented.

Our study intends to offer a deeper comprehension of how the homeostatic machinery of the auditory system copes with endogenous, *e.g.* age-related, or also exogenous, *e.g.* noise-induced perturbations. We aim to help create new tools, and recovery strategies that can protect the auditory system, not only of fruit flies, from damage.

Poster Ref: P3-C-020

Theme: C: Sensory and Motor Systems

Developing a brain computer interface for spinal cord injury patients: EEG translation and decision making based on intention of movement.

Syahrull Hi-Fi Syam Ahmad Jamil, Heba Lakany and Bernard Conway

University of Strathclyde

The majority of brain computer interface (BCI) studies are associated with healthy subjects and the systems operate based on a combination of multiple limbs movement. The acquired results are not an appropriate platform to fit the needs of neurologically impaired patients (*e.g.* spinal cord injury patients (SCI)) since healthy subjects have full control over their limbs and their associated electroencephalography (EEG) signature shows a normal pattern. SCI patients have limited or no control over their limbs and the EEG signatures are affected by the deafferentation and the cortical reorganization of the brain regions depending on the duration, level and type of injury. This study focuses on developing a BCI system for SCI patients based on wrist movement tasks in multiple directions. Prior to the experimental study on the targeted patient group, a pilot study consisting of 4 healthy subjects have been conducted. Participating subjects have performed and imagined performing right wrist movement in multiple directions using manipulandum and triggered by a visual cue whilst EEG, electromyography (EMG) and movement signals were synchronized and recorded simultaneously through NeuroScan Synamp system and Cambridge Electronic Design. The recorded signals were then processed and filtered using two types of spatial filter namely common average referencing and Laplacian referencing. The EEG signal was analysed using event related spectral perturbation (ERSP) and repeated measure of ANOVA and classified using k-nearest neighbour classifiers. The classification accuracy results of predicting intention to move for motor imagery and motor task dwell within the range of 70%-100%. Predicting both the intention and direction of movement, the classification accuracy lies between44.64%- 90%. The highest classification accuracy was contributed by high density electrodes and contra lateral electrodes using Laplacian spatial filter. These encouraging results show that the intention of rapid point-to-point right wrist movement to four different directions can be used to develop a robust BCI system that capable of operating on four different tasks.

Poster Ref: P3-C-021

Theme: C: Sensory and Motor Systems

Sync or wwim? Using a detailed computational model to investigate how the tadpole spinal cord can produce multiple patterns of motor activity.

Robert Merrison-Hort[1], Roman Borisyuk[1], Zhang Hong-Yan[2] and Li Wen-Chang[2]

[1]Plymouth University, [2]University of St. Andrews

Recent experimental findings show that the spinal cord of the *Xenopus* tadpole can produce both left-right anti-phase oscillations (swimming) and short bouts (up to about 1s) of in-phase synchronous activity [1]. Key to swimming and synchrony is a class of excitatory descending interneurons (dINs). It has been hypothesised that, due to commissural axonal delays, bouts of synchrony could be triggered by occasional mid-cycle spiking in dINs.

Since this hypothesis is difficult to test in real animals, we use biologically realistic anatomical and functional computational models, which represent a 1.5mm section of tadpole spinal cord containing ~1,500 neurons and ~85,000 synapses. Synaptic connectivity is determined by a model of axon growth [2], and the neuronal activity is simulated according to a conductance based (Hodgkin-Huxley) model. We have previously shown that this model can generate stable realistic swimming activity in response to simulated touch [3].

Our simulations show that injecting mid-cycle currents to groups of dINs reliably induces transient bouts of synchrony. As in real animals the frequency of synchrony is twice that of swimming. After a variable number of cycles of synchrony, or after slightly perturbing spike timing, activity instantaneously switches back to swimming. Slightly increasing the commissural axonal delay dramatically increases the stability of synchrony, producing networks that are tri-stable (quiescent, swimming, and synchrony states). Theoretical analysis of a reduced model allows us to investigate precisely how the stability of synchrony depends on the model's parameters.

[1] Li WC, Merrison-Hort R, Zhang HY, Borisyuk R: The Generation of Antiphase Oscillations and Synchrony by a Rebound-Based Vertebrate Central Pattern Generator. J Neurosci 2014, 34(17): 6065-6077
[2] Borisyuk R, Azad AK, Conte D, Roberts A, Soffe SR: A developmental approach to predicting neuronal connectivity from small biological datasets: a gradient-based neuron growth model. PLoS ONE 2014, 9(2): e89461
[3] Roberts A, Conte D, Hull M, Merrison-Hort R, Azad AK, Buhl E, Borisyuk R, Soffe SR: Can simple rules control development of a pioneer vertebrate neuronal network generating behaviour? J Neurosci 2014, 34(2): 608-21

Poster Ref: P3-C-022

Theme: C: Sensory and Motor Systems

Reticulospinal neurons play a key role in the recovery of voluntary locomotion in response to neuroprosthetic rehabilitation after a severe spinal cord contusion.

Cristina Martinez-Gonzalez, Lucia Friedli, Janine Beauparlant, Galyna Pidpruzhnykova, Laetitia Baud, Simone Duis and Gregoire Courtine

CNP/EPFL, Lausanne, Switzerland

We found that neuroprosthetic rehabilitation combining electrochemical neuromodulation of spinal circuits and robot-assisted training re-established supraspinal control of locomotion after a severe mid-thoracic contusion of the spinal cord in rats. Here, we pursued to identify the mechanisms underlying this functional recovery. Combination of anterograde and retrograde neuronal tract tracing revealed that the degree of functional recovery correlated with the amount of spared tissue and the degree of corticospinal, reticulospinal, and serotonergic fiber reorganization.

To demonstrate the key role of descending fiber reorganization in the recovery of supraspinal control of locomotion, we performed two sets of experiments. Firstly, we delivered deep brain stimulation in the midbrain locomotor region to activate reticulospinal fibers that were spared by the lesion. Continuous stimulation of the midbrain locomotor region near-instantly triggered coordinated leg movements and improved voluntary motor control capacities.

Secondly, we exploited a virus-mediated inactivation technique to temporarily and reversibly silence reticulospinal neurons with spared synaptic projections to lumbar spinal segment located below the injury. Inactivation of reticulospinal neurons in rats that previously regained voluntary locomotion produced a marked decline in gait performance. Our results demonstrate that neuroprosthetic rehabilitation actively promotes reorganization of spared reticulospinal fibers after a lesion, and that these projections significantly contribute to recover supraspinal control of locomotion during electrochemical neuromodulation of spinal circuits.

Poster Ref: P3-C-023

Theme: C: Sensory and Motor Systems

Optogenetic dissection of circuits mediating sensorimotor integration in the mouse whisker system.

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[1]Department of Physiology, Anatomy and Genetics, University of Oxford, [2]Janelia Farm Research Campus

Rodents actively move their whiskers to detect objects and construct spatial representations of their environment. Active sensation and sensorimotor integration depend on connections between sensory and motor systems. Here we aimed to functionally characterise the projections from vibrissal motor cortex (M1) to vibrissal somatosensory barrel cortex (S1) using optogenetics. Using extracellular recordings in anaesthetised mice, we found that optical activation of channelrhodopsin-2 (ChR2) in M1 inhibited a subsequent sensory response in S1 to brief deflection of the whiskers. In addition, preliminary extracellular recordings from the thalamus of anaesthetised mice also showed inhibition of a response to deflection of the whiskers following optogenetic M1 stimulation. To exclude the possibility that this inhibition originates within the cortex, whole-cell recordings were performed in acute slices of S1 from mice specifically expressing ChR2 in M1. However, optogenetic activation of M1 axons did not inhibit a subsequent response to electrical stimulation in different layers of S1, suggesting that thalamocortical circuits may underlie this mechanism of sensorimotor integration.

Poster Ref: P3-C-024

Theme: C: Sensory and Motor Systems

Biophysical and transcriptomic analysis of the auditory organ of closely related *Drosophila* species reveals mechanosensory and gene regulatory variation.

Ryan G Kavlie[(1)], Marina Navel Sanchez[(2)], Elena Martini[(1)], Stein Aerts[(2)] and Joerg T Albert[(1)]

[1]Ear Institute, University College London, [2]Center for Human Genetics, University of Leuven, Belgium,

Virtually all of our behaviour is enabled, guided and restricted by our senses. A variety of sense organs have evolved within the animal kingdom, which serve the extraction and pre-processing of information from the external physical world. However, the molecular mechanisms of sense organ specificity, especially in mechanosensation, and how these influence evolution remains unclear. We use *Drosophila melanogaster* and closely-related species to understand how mechanosensation, in particular hearing, drives reproductive isolation and evolution as well as to understand mechanosensation in general.

In *Drosophila*, the spectral tuning of the flies' antennal ears correlates with the spectral composition of song pulses produced by conspecific males as part of their courtship behaviour. Laser-Doppler vibrometric analysis of sound receiver mechanics and extracellular recordings of compound action potentials from the antennal nerve showed that this species-specific auditory tuning is, at least partly, the result of variations of the molecular modules for auditory transduction. In *Drosophila*, auditory transducers are located in ciliated dendrites of Johnston's Organ neurons in the second antennal segment.

We also analysed the Johnston's Organ transcriptomes of six closely-related *Drosophila* species using RNA-seq to identify gene expression differences between the auditory structures. Interestingly, Gene Ontology (GO) analyses of the most variably expressed genes showed their involvement in phototransduction and reproduction. The application of predictive bioinformatics (using i-cisTarget and iRegulon) on these auditory transcriptomes identified transcription factors potentially important for auditory function and many of their downstream targets (regulons) that may be responsible for the variation among the different species. Further experiments are underway to identify the functional significance of these regulons in hearing, mechanosensation and evolution.

Poster Ref: P3-C-025

Theme: C: Sensory and Motor Systems

An implantable neural stimulator to restore vestibular function in human patients.

Christopher Phillips, Leo Ling, Amy Nowack, Kaibao Nie, Jay Rubinstein and James Phillips
University of Washington, USA

Introduction: Loss of vestibular hair cell function results in imbalance, dizziness, and gaze instability. We have developed an implantable prosthesis to replace inner ear hair cells, and restore function in human patients.

Methods: In an initial safety and efficacy trial, we implanted a receiver stimulator into 4 human subjects suffering from vestibular loss. The device was a modified cochlear implant with three leads implanted adjacent to the ampullae of the semicircular canals. The implanted device communicated with an external processor *via* an RF link. The stimulator produced pulse amplitude and/or pulse frequency modulated trains of biphasic pulses to drive vestibular afferents. To evaluate the efficacy of stimulation, we monitored: 1) Eye movements recorded in subjects seated in a rotary chair, 2) body sway recorded in subjects standing on a posturography platform, 3) verbal report of perceived rotation, and 4) subjective visual vertical.

Results: Electrical stimulation with the implant that produced eye movements aligned with the stimulated canal did not produce pain, nausea, sounds, or facial nerve responses. Prolonged stimulation produced nystagmus with sustained slow phase eye velocity, and after-nystagmus. Stimulation pulse rate or amplitude changes modulated slow phase eye velocity. Eye movement responses were sustained over several test sessions, but responses decreased over time. Modulated electrical stimulation also modulated the gain and offset of the aVOR.

Electrical stimulation produced body sway largely aligned with the stimulated canal. Changes in head position changed the direction of sway. Modulation of pulse amplitude modulated sway amplitude.

Rotational percepts were produced by electrical stimulation. The perceived rotation was aligned with the stimulated canal. The velocity of the perceived rotation was related to the pulse amplitude of the stimulation, but did not match the eye velocity of responses recorded simultaneously. Electrical stimulation produced consistent changes in subjective visual vertical.

Conclusion: An implantable prosthesis was effective in driving largely appropriate responses in human subjects with vestibular loss.

Acknowledgements: NIH (NIDCD, NCRR, ORIP), Coulter FDN, Cochlear Ltd.

The fully implanted stimulator is a modified Freedom cochlear implant with 3 leads, one remote ground, and one case ground. There are 3 stimulation sites at the small (150 um diameter) tip of each lead, which are inserted through fenestrations in the bony labyrinth into the perilymphatic space adjacent to each semicircular canal ampulla in a single ear.

Poster Ref: P3-C-026

Theme: C: Sensory and Motor Systems

Neurons in the superior colliculus of mouse are sensitive to spatial and temporal visual context.

Gioia De Franceschi and Samuel Solomon

University College London

Extraclassical receptive fields modulate the response of visual neurons to stimuli within the classical receptive field, generally by suppressing response, and can help make them sensitive to spatial and temporal context. These 'suppressive surrounds' may play a role in constructing visual salience. Here we measure the spatiotemporal sensitivity of suppressive surrounds in the superior colliculus, an area thought important in the representation of salience. We made extracellular single-unit measurements from the superficial layers of superior colliculus in 15 urethane anesthetized mice. Response to drifting gratings was suppressed when the stimulus was enlarged beyond the classical receptive field in most neurons (35/41), and on average suppressed response by 41.7% (S.D. 28.5%). We then measured response to a small grating patch of optimal orientation, spatial and temporal frequency, in the presence and absence of annular gratings of varying orientation, spatial or temporal frequency. Suppression was tuned for temporal frequency in 21/31 neurons, where it was on average strongest near 4 Hz. Suppression was tuned for spatial frequency in 24/31 neurons, where it was maximal near 0.1 cycles/degree. Suppression was orientation tuned in 10/29 neurons, where it was strongest for orientations like that over the classical receptive field. Neurons displaying tuning in one dimension were not necessarily tuned along other dimensions. In conclusion, the responses of visual neurons in superior colliculus are sensitive to spatiotemporal context, and can signal the presence of spatial or temporal discontinuities. This context sensitivity may help in the selection of salient regions in the environment, and provide cues for subsequent analyses that rely on the segregation of objects from their background.

Poster Ref: P3-C-027

Theme: C: Sensory and Motor Systems

Firing dynamics and modulatory actions of supraspinal dopaminergic neurons during locomotor behaviour.

Michael Jay, Francesca De Faveri and Jonathan McDearmid

University of Leicester

The diencephalospinal dopaminergic pathway is a highly evolutionarily conserved supraspinal tract that has previously been implicated in both the development and modulation of vertebrate locomotor activity. However, despite the potential importance of this pathway to vertebrate motor control, the types of information encoded by supraspinal dopaminergic neurons and their relationship to motor network activity remain unknown. To address this, we have used *in vivo* patch clamping to study endogenous activity patterns of identified diencephalospinal dopaminergic neurons in awake, paralysed zebrafish larvae capable of producing behaviourally relevant activity patterns. Paired recordings reveal the relationship between diencephalospinal dopaminergic neurons activity patterns and locomotor output. Using targeted ablation of diencephalospinal dopaminergic neurons we find motor episode frequency, but not motor patterning, is strongly suppressed suggesting these cells may regulate spinal network excitability.

Poster Ref: P3-C-028

Theme: C: Sensory and Motor Systems

Restoration of locomotor circuit following spinal cord injury in simple aquatic animals.

Sofia Anagianni and Hong-Yan Zhang
University of Edinburgh

The ability to functionally restore spinal neural circuits following injury in mammals, including humans, has been mostly lost during evolution. However, many simple animals, such as *Xenopus* tadpoles and zebrafish can repair their central nervous system during development and even in adulthood; such animals provide ideal models for exploring the mechanisms of successful restoration of neuronal circuits. We are using both *Xenopus* tadpoles and zebrafish larvae to examine how their spinal neural circuits controlling swimming behaviour can be repaired following injury. Fast speed video recordings are used to evaluate the degree of locomotor deficit and monitor the recovery of their swimming behaviours. Animals are also immobilized in alpha-bungarotoxin, and their ventral root activities during fictive swimming are recorded using suction electrodes in order to explore the recovery of rhythmic locomotor output. Individual spinal neurons are recorded to compare their electrical properties following injury, reveal how different classes of neurons recover and their contribution to circuit function. Understanding the basic aspects of motor circuit repair following spinal cord injury can be crucial for further investigations on the mechanisms underlying neural circuit regeneration and functional restoration.

Poster Ref: P3-C-029

Theme: C: Sensory and Motor Systems

Stimulus information encoded in the local field potentials of both the lateral geniculate nucleus and the primary visual cortex is modulated by brain state.

Silvia Ardila-Jimenez, Jiaying Tang and Simon Schultz

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Neuronal oscillations in the form of Local Field Potentials (LFP) reflect summed population activity of local networks (Buzsaki, *et al.* 2012). LFPs responses of sensory networks are known to be dependent of global brain state, local network activity, and visual stimuli. In anaesthetised preparations the level of anaesthesia mimics these naturally occurring changes. Here we examine how different levels of anaesthesia impact visual stimulus information, as quantified by their mutual information, both in the dorsal lateral geniculate nucleus (LGN) and in the primary visual cortex (V1) of mice. By changing the level of anaesthesia we reliably produce changes in LFP responses in both areas consistent with synchronised/sleep-like (deep) and desynchronised/awake-like (light) states. In the deep anaesthesia level mutual information appears to have a broader spectrum in both the LGN and the V1. While in the light anaesthesia condition relevant stimulus information is concentrated in the gamma band, more specifically in the 40 to 50Hz range. This is consistent with gamma band activity being stimulus induced (Nase, *et al.* 2003). The changes in the responses in the gamma band between the deep and light levels of anaesthesia are unlikely to be due to increased power at that frequency as the average power changes very little between conditions. In the cortex stimulus information shows a layer dependent structure; layers 2/3 appear to be the most informative of the stimulus. In the LGN there is no clear structure. These structural characteristics are expected given physiological structure of these areas in the mouse.

Poster Ref: P3-C-030

Theme: C: Sensory and Motor Systems

Integration of multiple visual pathways in the blowfly.

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The stabilization of gaze may involve multiple sensory systems. In blowflies, the reflex depends on input from the compound eyes, ocelli, halteres and campaniform sensilla located on the wings to provide input for the reflex. Individually, the corresponding pathways involved cover different dynamic input ranges, incur different processing delays, and suffer from different levels of sensor and processing noise. Information from multiple sensory pathways must be integrated in order to effect appropriate movements of the head to stabilize gaze, however it is not entirely clear how this happens.

We investigated the combination of information from the two visual pathways contributing to gaze stabilization: the motion vision pathway provided by the compound eyes, and the ocellar pathway, measuring light intensity changes in the dorsal visual hemisphere due to attitude changes. Using high speed videography we measured compensatory rotations of the head in response to a simulated roll rotation of a false-horizon around the fly, oscillating at up to 10 Hz. We applied a linear systems analysis to obtain the individual frequency responses for the two pathways. We found that the ocellar input reduces the response delay by an average of 5 ms but does not significantly affect the response gain or bandwidth. Our result suggests a non-linear integration of compound eye and ocellar information.

We are now performing intracellular recordings from elements along the visuo-motor pathway likely to be involved in the integration of motion vision and ocellar signals, in response to the same visual stimulus used to evoke head movements in our behavioural experiments. This will allow us to study how signals induced by a common visual input, and affected by different processing delays along the two visual pathways, are combined to ultimately reduce the delay in the behavioural output.

Theme D: Learning, Memory and Cognition

Posters P3-D-001 to P3-D-060

Poster Ref: P3-D-001

Theme: D: Learning, Memory and Cognition

Investigating the spectrum of cognitive impairment in multiple sclerosis using touchscreen cognitive testing.

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Background: Multiple sclerosis (MS) is a CNS demyelinating syndrome characterised by physically disabling symptoms. Cognitive impairment, which potentially impacts on quality of life, is generally under-recognised and incompletely evaluated, partly due to the lack of efficient tests available for use in the clinic. Despite this, cognitive deficits have been reported in up to 70% of patients when specifically assessed.

Aims: To investigate the spectrum of cognitive impairment, and potential confounding factors for deficits, in patients with MS reviewed in an outpatient clinic using validated Cantab neuropsychological tests administered by touchscreen.

Methodology: Consecutive patients presenting to a specialist MS clinic over a 6 month period were assessed. Working Memory (WM), Executive Functioning (EF), Processing Speed (EF), Attention (AT) and Episodic Memory (EM) were evaluated using Cantab neuropsychological tests on a touchscreen platform. Performance was adjusted for age, sex and educational level based on a large normative database. Duration of disease, type of MS, severity of disease, sedating medications, and severity of depression were correlated with the presence and severity of cognitive deficits.

Results: 105 consecutive patients (mean age 44.6y ± 10.8, range: 22-70y) were assessed with a spectrum of disease duration, severity and type. The most frequent cognitive domain affected in all patients with MS was EF (in 24.7%), followed by WM (22.7%), PS (17.2%), EM (17.6%) and AT (6.1%). Single domain cognitive impairment was identified in 23.5% of patients and multi-domain deficits in 25.9%. Disease severity was associated with deficits in WM, EF, PS and AT. Severity of depression correlated with deficits in EF, WM and PS.

Conclusions: Results from this study confirm cognitive impairment is common in patients with MS. Furthermore, impairment occurs across a range of domains and correlates with severity of disease, although is independent of factors such as age, duration of disease, and type of MS. Routine cognitive assessment is recommended as part of holistic assessment in multiple sclerosis. Computerised testing provides a novel and efficient method for patient evaluation.

Poster Ref: P3-D-002

Theme: D: Learning, Memory and Cognition

α7 and α4β2 nicotinic receptors in the prefrontal cortex control different aspects of associative recognition memory in rats.

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The medial prefrontal cortex (mPFC) is essential for associative recognition memory, and is known to rely on cholinergic transmission through muscarinic acetylcholine receptors. However, the contribution of prefrontal nicotinic acetylcholine receptors (nAChR) to this process is not known. The presented work investigates the involvement of the two major nAChR subtypes, homomeric α7 and heteromeric α4β2 receptors, within the mPFC for associative recognition.

Associative recognition memory performance was assessed using an object-in-place behavioural task, which tested the subject's ability to combine object and spatial information. A cohort of rats were surgically implanted with intra-cerebral cannula to enable local perfusion of compounds into the mPFC. Subtype selective antagonists were administered prior to sample or test phases of the task to investigate the role of nAChRs in associative memory acquisition and retrieval, respectively.

The data presented reveals a delay-dependent effect of α7 nAChR antagonism in memory acquisition, with deficits arising after 24hours but not at shorter delays of 5min or 1hour ($p < 0.05$*). Impairments were not seen with α7 nAChR antagonism during retrieval. The opposite pattern of deficits was seen for α4β2 nAChRs, with antagonist administration significantly impairing 24hr-delayed memory retrieval ($p<0.05$*), but not acquisition. Statistical analysis showed a significant interaction between infusion, nAChR subtype, and memory process ($p<0.01$**).

The contrasting pattern of impairments seen with inactivation of the two nAChR subtypes provides evidence for distinct roles of α7 and α4β2 nAChRs within different stages of associative recognition memory. Furthermore, the temporal dependence of α7 nAChR activation, with antagonism causing deficits only in the acquisition of longer term memories, is suggestive of an involvement of α7 nAChR which becomes requisite only as the memory load increases. Preliminary work is currently being conducted using *in vitro* electrophysiology to investigate the potential cellular mechanisms that may underlie the behavioural effects of nAChR.

Poster Ref: P3-D-003

Theme: D: Learning, Memory and Cognition

Effect of neurogenesis reduction on spatial cognitive flexibility in active allothetic place avoidance task.

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The first aim of this study was to find an optimal dose of cytostacic Temozolomide (TMZ) for effective reduction of adult hippocampal neurogenesis with minimal health side effects. Second aim was to determine the influence of reduction of neurogenesis on spatial cognitive flexibility in Active Allothetic Place Avoidance task (AAPA).

In TMZ-dose experiment rats were divided into four groups which recieved four week TMZ treatment (10, 25 and 40 mg/kg) and a control group. To detect level of neurogenesis cells were labeled by bromodeoxyuridine (BrdU). Numbers of BrdU+ cells were counted using stereologic principles. During the experiment blood element counts and body mass was monitored along with sensorimotoric tests. The results indicate that dose of 10 mg/kg reduces neurogenesis by 64 %, dose of 25 mg/kg reduces neurogenesis by 75% and dose of 40 mg/kg reduces neurogenesis by 90%. Body mass and number of leukocytes was reduced in groups treated with 25mg/kg and 40mg/kg of TMZ. TMZ application did not affect sensorimotoric performance.

Dose of 10mg/kg was designated as optimal in the light of absence of confounding side effects and adequate neurogenesis reduction. Dose of 10mg/kg was selected for testing in AAPA task. In this task animal had to avoid an unmarked sector of a circular rotating arena. Upon entering, animal received a gentle aversive stimulus. To-be-avoided sector did not rotate with the arena; therefore animals had to move constantly to avoid being dragged there by arena rotation. Compared to the Morris ware maze, animal does not require sense of detail to solve the task, but a comprehension of it. Each animal underwent one 20 minute acquisition session a day for 5 days. Five 20 minute reversal sessions followed with forbidden sector relocated to the opposite side of arena. In rats receiving a dose of 10 mg/kg TMZ there was no apparent deficit in solving this task. Negative finding with a dose 10 mg/kg (64% neurogenesis reduction) was confirmed by absence of effect even after administration of higher dose of TMZ (25mg/kg, 75% neurogenesis reduction). We conclude that neurogenesis reduction doses not affect cognitive flexibility in this dry maze paradigm.

Poster Ref: P3-D-004

Theme: D: Learning, Memory and Cognition

Increased impulsivity in the stop-signal reaction time task in a mouse model of Prader–Willi syndrome: role of 5-HT2C receptor.

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Prader–Willi syndrome (PWS) is a neurodevelopmental disorder caused by deletion or inactivation of paternally expressed imprinted genes on human chromosome 15q11-q13 leading to an array of disabilities including compulsive hyperphagia and deficits in social behaviour, such as social withdrawal, temper tantrums, perseverative speech and behaviour, mental rigidity, stereotyped behaviour and impulsiveness. The PWS genetic interval contains several brain-expressed small nucleolar (sno)RNA species. One of these, Snord115, negatively regulates editing and alternative splicing of the 5-hydroxytryptamine (5-HT) 2C receptor (5HT2CR, encoded by Htr2c) pre-RNA which is key regulator of behavioural inhibition and impulsivity1,2. We have used the imprinting centre (IC) deletion mouse model for PWS (PWS-IC), which results in a loss of all paternal gene expression for the PWS interval3, including Snord115, and leads to an increase abundance of less functional isoforms of Htr2c. Previously, we found no baseline effect of IC deletion on premature responding in the five-choice serial reaction time task (5-CSRTT)3. However, an augmented increase in impulsivity was seen in PWC-IC mice relative to wild-type (WT) when the behaviour in this task was probed with 5-HT2CR selective drugs. Here we extend study of impulsivity in PWS-IC mice, by examining behaviour in the stop-signal reaction time task (SSRTT)2. All mice showed the anticipated increase in impulsive responding as the stop-signal was moved closer to the end of the go response, but PWS-IC mice demonstrated increased baseline impulsivity relative to WT at all stop-signal positions. Furthermore, administration of 5HT2CR agonist (WAY-161503) did not alter WT responding, but made PWS-IC mice less impulsive. These data, in comparison with our previous work3, suggest specific facets of inhibitory behaviour may be impaired in PWS-IC mice and that variation in 5-HT2CR may mediate this dissociation.

References

1. Psychopharm. 176(3-4):376-85
2. Neuropsychopharm. 38(11):2150-9
3. Hum. Mol. Genet. 18(12):2140-8

Poster Ref: P3-D-005

Theme: D: Learning, Memory and Cognition

The role of DNA in hippocampal-dependant memory systems: implications for trauma processing and navigation performance.

Jessica Miller and Jan Wiener

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Bournemouth University (in collaboration with Prof Chris Brewin and Combat Stress) investigates the role of the Brain Derived Neurotrophic Factor (BDNF) gene in hippocampal-dependent processing of traumatic memories and spatial information. The study (n=154) considers trauma exposure from combat and police service and implements: the PTSD Diagnostic Scale; validated navigation questionnaires; a hippocampal-dependent virtual reality way-finding task (Wiener *et al.* 2013) and the 4 Mountains Task (Hartley *et al.* 2007).

A diverse literature (Miller and Wiener, 2014) suggests that PTSD is inextricably linked to the hippocampus (Pitman *et al.*, 2012) and that hippocampal integrity has a strong genetic component, relevant to stress and navigation (Gatt *et al.*, 2009; Lovden *et al.*, 2011). The value of applying hippocampal processing to PTSD therapy has been specifically proposed (Brewin and Burgess, 2014).

Initial findings from the BU study (2015) demonstrate that PTSD hinders navigation performance, and that neither age-related nor combat trauma-related navigation performance decline can be predicted with existing navigation questionnaires. Data also suggests that: BDNF gene variation may predispose individuals to drop hippocampal-dependent spatial processing after trauma exposure (independent of clinical PTSD); and that spatial information processing bias may negatively affect PTSD treatment success.

References

Brewin, C. and Burgess, N. (2014) Contextualisation in the revised dual representation theory of PTSD. J Behav Ther Exp Psychiatry. 45(1)

Gatt, *et al.* (2009). Interactions between BDNF and early life stress predict brain and arousal pathways to syndromal depression and anxiety. Mol Psychiatry.14.

Hartley, *et al.* (2007). The hippocampus is required for short-term topographical memory in humans. Hippocampus 17.

Lövdén, *et al.* (2011). Performance-related increases in hippocampal NAA induced by spatial navigation training are restricted to BDNF homozygotes. Cerebral Cortex 21, 6.

Miller, J.K. and Wiener, J.M. (2014) PTSD recovery, Spatial Processing, and the val66met Polymorphism, Fronts in Hum Neurosci, 8, 100.

“Hippocampal integrity and hippocampal-dependent information bias have implications for combat trauma processing and navigation performance in theatre (UK Marine image courtesy of Daily Mail 2011)”

Poster Ref: P3-D-006

Theme: D: Learning, Memory and Cognition

Cognitive resilience and a potential neural compensatory mechanism.

Anya Topiwala[1], Claire Sexton[2], Nico Filippini [1], Eniko Zsoldos[1], Abda Mahmood[1], Charlotte Allan[1], Archana Singh-Manoux[3,4], Mika Kivimaki[3], Clare Mackay[1] and Klaus Ebmeier[1]

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Background: The relationship between Alzheimer's disease pathology and cognition is not linear. Resilient individuals can tolerate a degree of brain change whilst maintaining cognitive function. The neural mechanisms for this are poorly understood.

Methods: Community-dwelling participants in the Whitehall II study, University College London, underwent detailed neuropsychological testing and multi-sequence 3T brain MRI in the Imaging sub-study at the University of Oxford. Principle components analysis (PCA) extracted common factors from the cognitive tests. The relationship between IQ and cognitive factors was examined using multiple regression. FMRIB's Software Library Tract Based Spatial Statistics generated fractional anisotropy (FA) values for white matter integrity. These were correlated with IQ (adjusted for age, sex, education, and Framingham risk score (FRS)). Additionally, subjects were divided into quartiles based upon normalized hippocampal size. FA was correlated with cognitive factors for each quartile group.

Results: 363 participants (mean age 69.3 years) were included (58 excluded due to major neurological disorders/missing data). FA was significantly correlated with IQ score in a widespread distribution, after adjustment for confounders. PCA identified memory and speed cognitive factors. The relationship between IQ and these factors was strongest at mild-moderate levels of hippocampal atrophy (HA). Whilst the speed factor was correlated with FA across all hippocampal sizes, memory was only correlated with FA at mild-moderate levels of HA.

Conclusions: High premorbid IQ is protective against cognitive impairment and correlated with WM integrity. Memory becomes dependent on WM integrity when mild Alzheimer's pathology is present. WM tracts may mediate a compensatory mechanism ensuring resilience.

Poster Ref: P3-D-007

Theme: D: Learning, Memory and Cognition

Consolidation of prospective memory: the effect of sleep on completed and reinstated intentions.

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Sleep facilitates the consolidation of new memories, especially of memories that are relevant for the future. Recently, we found that sleep improves prospective memory performance after a delay of two days. In this study, subjects learned a set of cue-associate pairs and were instructed that they would have to detect the cue words and write down their associates within a lexical decision task (serving as ongoing task) two days later. Following the learning session, subjects either slept or stayed awake for one night. After a second (recovery) night, sleep participants detected more cue words and remembered more associates than wake subjects. Based on these results, we asked whether the enhancement of prospective memory by sleep would be preserved if the intention was completed before sleep and whether completed intentions could be reinstated for sleep-dependent consolidation.

In Experiment I, using the same task and design as in the original study, subjects learned the cue-associate pairs in the evening and were instructed that testing would take place after two hours before a night of sleep or wakefulness. Two days later, a second surprise test took place. The results show that sleep and wake subjects did not differ in prospective memory performance at this test, suggesting that sleep does not facilitate the consolidation of prospective memories if the intention is completed before sleep.

In Experiment II, using the same setup as in Experiment I, the intention was reinstated after the first test session in the evening by instructing the participants about the second test session. At this second test, the sleep and wake group again did not differ in performance, suggesting that reinstating the intention after its completion is not sufficient for a sleep benefit.

Finally, in Experiment III, subjects were instructed about both test sessions (in the evening and two days later) immediately after learning. This time, prospective memory performance of sleep subjects after two days was superior to the performance of the wake subjects.

Together, these data suggest that for intentions to benefit from sleep, they (i) have to be induced in temporal proximity to the initial learning session, and (ii) subjects have to expect the test session to take place after sleep.

Poster Ref: P3-D-008

Theme: D: Learning, Memory and Cognition

Testing the inter-parietal hemispheric balance account of visual extinction by combining TMS and fMRI.

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Donders Institute for Brain, Cognition and Behaviour - Radboud University, Netherlands

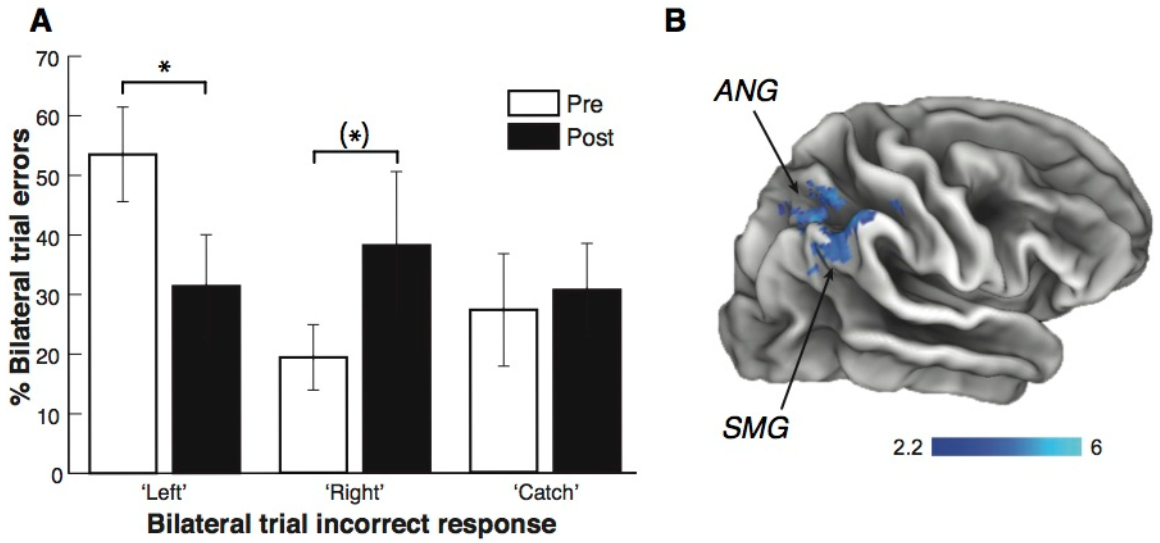
Following right parietal cortex damage patients can often detect a unilateral stimulus presented to left or right, but when presented bilaterally the stimulus on the right 'extinguishes' that on the left from awareness. Extinction is thought to arise from disrupted inter-hemispheric balance between attentional signals in left and right parietal cortex. Theoretical models posit that attentional vectors in each parietal cortex direct attention to contralateral space. In a healthy brain, these counterbalance one another. Right parietal damage disrupts this balance, weakening leftward attention and strengthening rightward attention, causing extinction when stimuli compete.

We aimed to test this physiological model directly in the healthy brain using transcranial magnetic stimulation (TMS, 1Hz 15 min.) to transiently suppress activity in the right angular gyrus (rANG), and functional magnetic resonance imaging (fMRI) to image the functional consequences while participants performed a visual extinction task. A first psychophysical experiment (n=5) confirmed that rANG TMS could induce extinction-like behaviour: overall accuracy was unchanged, but after TMS the spatial distribution of bilateral errors shifted significantly from left to right (Figure 1A).

In the fMRI experiment (n=12), TMS did not affect behaviour, making it possible to attribute activation changes directly to stimulation, rather than strategy shifts. Voxel-wise random effects analysis showed that TMS changed the balance of inter-hemispheric fMRI activity between left and right parietal cortex.

TMS induced a significant leftward shift in inter-hemispheric dominance in dorsal and ventral parietal cortex (Figure 1B). Across individuals, the greater participants' baseline right parietal dominance, the greater the effect of TMS. The effect was specific to parietal cortex, was present on all trial types (unilateral and bilateral), and was consistent with stimulation causing a rightward shift in spatial attention during the cue period, rather than a specific effect on bilateral target processing, as might have been predicted.

To our knowledge this is the first direct physiological test of the inter-hemispheric competition account of visual extinction in the healthy brain.



Behavioural and imaging results.

[A] Percentage errors made on bilateral trials distributed across incorrect response types before and after rANG TMS (N = 5, Error bars = 1 SEM).

[B] Regions showing a leftward shift in inter-hemispheric dominance after rANG TMS. (N=12; t(11)>2.2, corrected cluster extent significance threshold $p<0.05$). ANG: Angular gyrus, SMG: supramarginal gyrus.

Poster Ref: P3-D-009

Theme: D: Learning, Memory and Cognition

Acute effects of interferon on global and regional function brain connectivity.

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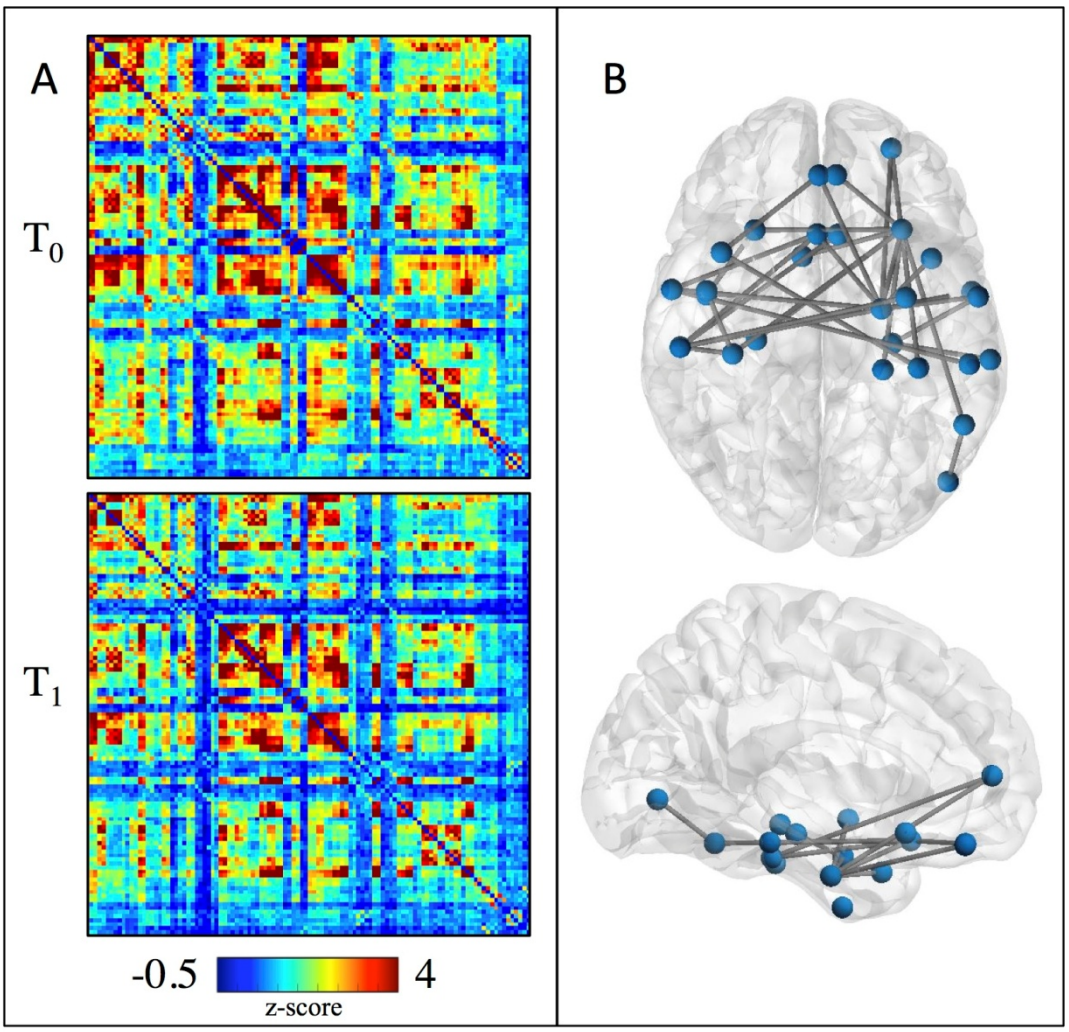
Introduction: Systemic inflammation impairs mood, cognition and behaviour and is increasingly implicated in the etiology of common mental illnesses. Pro-inflammatory cytokines are among the principle mediators of these immune influences on the brain and when given clinically rapidly induce fatigue and deterioration in mood. Though inflammation has been shown to modulate activity within discrete brain regions their effects on global and regional functional connectivity and relationship to symptoms have not been investigated.

Methods: Twenty-two patients (48.9±11.3yrs, 15 male) with Hepatitis-C infection underwent resting-state fMRI (TR=2520ms; TE= 43ms; resolution:3×3×3.56mm; 34 axial slices; 190 volumes) at baseline (T0) and 4 hours after their first interferon-alpha (IFN) injection (T1). High-resolution T1-weighted image was also acquired. Fatigue was measured at each time point and for the 6 months duration of treatment using a Visual Analog Scale (VAS-f). After pre-processing with FSL, 112 nodes were defined using the Harvard-Oxford whole brain anatomical parcellation atlas. Maximal overlap discrete wavelet transform was then applied to decompose the corresponding time series into four frequency scales and the wavelet correlation coefficients at the low-frequency scale range (0.036-0.099 Hz) (Lynall ME *et al.*, 2010) used to construct a 112x112 functional connectivity matrix for each subject at T0 and T1. Differences between the two conditions were evaluated with the Network Based Statistic toolbox.

Results: Figure 1A shows the functional connectivity matrices averaged for all patients at T0 and T1. IFN was associated with significant decrease in functional connectivity ($p<0.05$ corrected for multiple comparisons) within a predominantly frontal - subcortical network as shown in 1B.

Discussion: Early results demonstrate a marked reduction in functional connectivity within a predominantly frontal - subcortical network post IFN. This is in keeping with published FDG-PET and fMRI studies showing predominant effects of chronic IFN on basal ganglia metabolic activity and reactivity. Ongoing work is evaluating effects of IFN on graph theoretic metrics of global and local efficiency and will investigate their relationship to IFN-induced fatigue.



(A) Functional connectivity matrices for the frequency range 0.036-0.099 Hz, averaged across all participants before (T0) and 4 hours after Interferon-alpha (T1). Colour denotes z-score. (B) Representation of functional connectivity reduction after Interferon-alpha.

Poster Ref: P3-D-010

Theme: D: Learning, Memory and Cognition

The development of a new diagnosis test for simultanagnosia using eye-tracking exploration of dynamic scenes.

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Simultanagnosia is a neurological disorder caused by bilateral lesions to the occipitoparietal brain regions. The disorder causes an inability to attend to more than one object or one feature at once. The ambition of this project was to create an ecological diagnosis tool to investigate patterns of visual exploration in normal perceivers and patients with simultanagnosia while looking at everyday scenes. The scenes were manipulated by having a neutral or busy background, having 2 or 3 actors present in the scene, and by having the actors interacting with each other or not. We administrated homemade videos to 40 control participants (24 women, mean age: 21.4). The principal aim of the study was to create norms from which to investigate a patient with simultanagnosia. The participants were asked to simply look at the videos, so that they could describe what they saw at the end of each scene. Presentation order of the scenes was randomized. Participants' eye movements were recorded using an Eyelink 1000 eye-tracking device. The eye tracking analyses consisted of measuring the proportion of total fixation time to regions of interest within each scene. We defined these regions in accordance to the relevant elements of the scene (*e.g.*, the position of the actors, and the area of interaction). The results showed that participants' attention to the scene was moderated by the number of actors, and by their interactivity. However, there was no significant effect of the background manipulation. The results are discussed in terms of the creation of a new diagnosis test for patients with simultanagnosia.

Poster Ref: P3-D-011

Theme: D: Learning, Memory and Cognition

Chronic pre-treatment with saline or fluoxetine on anxiety response in a radial arm maze.

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In a 3D maze, which is a modified version of the radial arm maze, avoidance of the distal segment of the arms is used as an indicator of anxiety. Balb/c mice require four to five sessions to venture onto the distal segments of the maze while C57/BL6J and CD-1 mice require one to two sessions, respectively.

In the present study, we examined the effect of chronic pre-treatment with fluoxetine (20 mg/kg) in BALB/c mice. The experiment involved 3 groups of mice. Two separate groups received either i.p. saline (SALCH) or fluoxetine (FLUCH) for two weeks, and were continued to be injected 30 min before exposure to the test apparatus during the subsequent 3 test days. The third group received i.p. saline (SALAC) 30 min before each test session.

The maze (Grey PVC, 5 mm thick) consists of nine arms radiating from a central platform. Each arm (51 cm x 11.2 cm) is made from two segments, extended from a nonagonal shaped central hub. The first segment of an arm (15.2 cm x 11.2 cm) directly attached to the central platform can be tilted and constitutes a bridge that allows access to the second segment (35 cm x 11.2 cm) of the arm. In the present experiment, the bridge to each arm forms a slope which is inclined upward by about 40º. All parts of the maze apparatus are unprotected; hence mice are exposed to a complete open space.

Both SALCH and FLUCH mice crossed onto the arms of the maze on their first exposure to the test, and the number of crossings increased in subsequent sessions. The number of crossings onto the arm was significantly high in session 1 ($p<0.04$) and low in session 3 ($p<0.05$) in FLUCH compared to SALCH. SALAC mice avoided the arms in each test session. There were no differences between groups in the number of crossings onto the bridges of the maze ($p>0.10$).

The present results indicate that chronic pre-treatment with saline or fluoxetine reduced significantly the avoidance of the distal arms of the maze, suggesting a decreased anxiety in these groups. However, such reduction in anxiety is likely to be due to the effect of handling during the repeated pre-treatments of mice.

Poster Ref: P3-D-012

Theme: D: Learning, Memory and Cognition

Withdrawn

Poster Ref: P3-D-013

Theme: D: Learning, Memory and Cognition

Learning and lateralisation shifts - a functional transcranial Doppler ultrasonography study.

Amy Spray and Georg Meyer

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Background: Musicians have been shown to draw on an extended network of shared brain areas when processing music and language. The current study looks at whether this is the result of a predisposition or the result of learning.

Results are presented from two studies: Firstly a between-subject design is utilised in which brain lateralisation patterns are measured for a language and a music generation task: Cued word generation and music synthesis. This was carried out between a group of musically trained individuals and a group of novices.

Secondly a within-subject design is used to compare the brain lateralisation patterns for the same word generation task and a music perception task (polyrhythm recognition). This was done with individuals before and after they have undergone a short duration of musical training (30 minutes of learning to tap polyrhythms).

Methodology/Principal Findings: Using functional transcranial Doppler ultrasonography (fTCD), we measured brain blood flow lateralisation patterns (hemodynamics) in our subjects.

We report two main findings:

1. We show highly correlated hemodynamics between both tasks in both experiments however only for participants who have undergone musical training; either prior to the study (experiment 1) and as part of the study (experiment 2).
2. The degree of improvement on the musical perception task (an indication of the level of learning) was significantly correlated with degree of lateralisation change.

Conclusions/Significance: These findings suggest that the recruitment of common circuity for music and language tasks is the result of learning. Moreover, it seems that even a short duration of musical training (just 30 minutes) is sufficient to cause this common recruitment. Finally the results suggest that the extent to which a task has been learnt can be quantified and observed in terms of lateralisation shifts.

Moreover, these shifts in lateralisation could indicate the utalisation of a new processing mechanism or may potentially constitute the beginnings of microstructural changes.

Poster Ref: P3-D-014

Theme: D: Learning, Memory and Cognition

Genes to cognition (G2C): Analysis of high-throughput behaviour data from 60 mouse mutant lines.

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Successful perception of and interaction with the environment are principal aspects of cognition and are key for survival of all freely moving animal species. These elements involve a diverse repertoire of innate/instinctive and adaptive/learned responses, in which deficits define disease states, but whose genetic architecture is largely unknown.

The G2C programme was a pioneering large scale neuroscience programme addressing the genetic architecture of cognition by measuring the impact of 60 engineered mouse mutations on a broad repertoire of behaviour measures related to perception of and interaction with the environment. One hundred and five original measures of mouse behaviour were summarised into a non-redundant set of 16 minimally correlated measures, which were therefore maximally statistically independent.

Sixty lines of mice carrying engineered mutations in 54 synaptic genes were examined in five standardised tests with respect to innate and learned responses to the environment. The 16 summary behaviour measures, describing innate/instinctive and learned responses, were altered in mutant mice. Combining these, innate/instinctive deficits were correlated with adaptive/learning deficits, and synaptic protein abundance predicted overall behavioural effects. Fourteen mutations resulted in stereotyped behaviour in mutants. Finally, IQ deficits associated with human mutations were correlated to behavioural effects of the knockout mutations in their orthologous mouse genes.

Our standardised observations from a large multi-mutant behaviour experiment embody a postsynaptic model of behaviour and disease and set new standards for multi-mutant phenotyping approaches.

The G2C analysis results and raw data files are freely available without login from www.genes2cognition.org.

Poster Ref: P3-D-015

Theme: D: Learning, Memory and Cognition

Post-traumatic amnesia: Disconnection between the medial temporal lobe and default mode network.

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Introduction: Post-traumatic amnesia (PTA) is very common early after traumatic brain injury (TBI). PTA is characterised by a confused, agitated state and a pronounced deficit in the ability to encode new memories. Its pathophysiology is poorly understood. The medial temporal lobe is central to memory processing, and normally shows strong functional connectivity to nodes within a large-scale intrinsic connectivity network, the default mode network (DMN). We hypothesise that a functional disconnection of the medial temporal lobe from the DMN will be present in patients with acute PTA.

Methods: Functional magnetic resonance imaging (MRI) was acquired from 15 healthy controls, 7 TBI patients without PTA and 8 patients in profound PTA. The presence of memory impairment (i.e. PTA) was assessed with the use of the Paired Associative Learning (PAL) task as part of the Cambridge Neuropsychological Test Automated Battery (CANTAB) computerised tool. Patients were investigated within two weeks of their injury. All data were analysed using FSL. Resting state data preprocessing included realignment of functional images, spatial smoothing using an 8 mm full-width at half-maximum Gaussian kernel. Functional images were registered to standard MNI space using the participant's high-resolution T1. Changes in functional connectivity between a central node of the DMN, the posterior cingulate cortex (PCC), the hippocampus and parahippocampus were assessed using a dual regression approach.

Results: Patients with PTA demonstrated significantly reduced functional connectivity between the parahippocampus and the PCC compared to controls. This reduction in functional connectivity was found to be related to impairments in associative memory. Functional connectivity with the hippocampus did not show any significant group differences.

Conclusions: The results suggest that functional disconnection between brain regions involved in memory processes, including nodes within the DMN, may underlie the profound cognitive impairments seen in PTA.

Poster Ref: P3-D-016

Theme: D: Learning, Memory and Cognition

Neurocognitive investigation of episodic memory impairment in obesity.

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Obesity has become an international health crisis. There is accumulating evidence that excess bodyweight may be associated with brain abnormalities and cognitive deficits. In particular, research suggests that obesity is associated with hippocampal and frontal dysfunction, suggesting an impact on episodic memory function. Here we present two experiments. In the first, young, otherwise healthy overweight individuals were found to be impaired relative to matched controls on a 'what-where-when' episodic memory task that required recollection of integrated temporal-spatial event details. Performance of the overweight participants was reduced across all levels of difficulty, precluding an explanation in terms of cognitive load. In a follow-up fMRI study, obese and lean participants completed the same 'what-where-when' task in the scanner. Key areas of the core recollection network in the brain, including the hippocampus, angular gyrus and prefrontal cortex, showed significantly reduced activity during performance of the 'what-where-when' memory test in obese participants relative to lean matched controls. Analysis of blood samples revealed that variance in brain activity in these memory areas was significantly predicted by fasting plasma insulin levels, but not by triglycerides or leptin. The differences in activity between the lean and obese groups were not entirely explained by group differences in insulin levels, however, suggesting that both adiposity and insulin influence brain activity during episodic memory encoding and retrieval. Implications are discussed for cognitive and neural models of obesity.

Poster Ref: P3-D-017

Theme: D: Learning, Memory and Cognition

Patients with minimal hepatic encephalopathy show increased oxidative stress correlating with cognitive and motor impairment.

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Aims: Cirrhotic patients may suffer minimal hepatic encephalopathy (MHE), with mild cognitive impairment. 3-Nitro-tyrosine levels are increased in serum of patients with MHE compared with patients without MHE and are a good biomarker for diagnosis of the cognitive impairment and MHE in cirrhotic patients. This suggests that oxidative stress could be involved in the induction of cognitive and motor alterations in MHE. The aims of this study were to assess 1) if oxidative stress is increased in patients with MHE compared to patients without MHE; 2) if oxidative stress correlates with the neurological alterations in MHE.

Results: Patients with MHE showed increased oxidative stress in blood compared to patients without MHE, with increased lipid peroxidation, DNA oxidation, protein carbonylation, 3-nitrotyrosine and GSSG/GSH ratio, and reduced GSH levels. The activities of antioxidant enzymes were enhanced in erythrocytes and mononuclear cells from patients with and without MHE compared to control subjects. Only glutathione peroxidase activity was increased in MHE patients compared to patients without MHE. Oxidative stress markers in blood, especially GSSG/GSH ratio, GSH, malondialdehyde and 3-nitrotyrosine, correlate with deficits in attention and motor coordination.

Innovation: These results suggest a relevant role of oxidative stress in the cognitive and motor alterations in patients with MHE.

Conclusion: The increase in antioxidant activities in patients would be an adaptive mechanism to cope with enhanced oxidative stress, although it is not effective enough to normalize it. Increased peroxynitrite formation could mediate the synergistic effects of hyperammonemia and inflammation on cognitive and motor impairment in MHE.

Poster Ref: P3-D-018

Theme: D: Learning, Memory and Cognition

Reliability of the ultimatum game: Implications for developing interventions for social cognition.

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Background: The Ultimatum Game (UG) is a task increasingly used in cognitive neuroscience to investigate prosociality, self-interest, and responses to (un)fairness. While fMRI, TMS and tDCS have been used to study the neural basis of task behaviour, modulation of performance would provide further insights into its neural underpinnings and provide input into potential treatment targets for patients with social cognitive deficits. Such approaches require that performance stability is known so that appropriate designs of adequate power can be planned. We have carried out a test-retest reliability study to aid design and interpretation of future modulatory studies of the UG.

Methods: 15 participants acted as responders in two sessions of an adapted version of the UG, separated by at least one week. This version of the UG differs from the traditional UG by including first-party (FP) and third-party (TP) conditions, and hyper-fair offers (>50%). We collected the following: rejection rates, fairness ratings, offer expectations, UG proposals, Dictator Game (DG) proposals. We used the intraclass correlation coefficient (ICC) as a measure of reliability. An ICC greater than 0.6 was considered reliable.

Results: Rejections rates largely showed good test-retest reliability, with the exception of TP hyper-fair offers. UG and DG proposer behaviour showed strong test-retest reliability. Offer expectations were stable across sessions, while offer fairness ratings were reliable, with the exception of very low offers.

Conclusion: We provide evidence that the Ultimatum Game is largely stable across sessions. This has important implications for the design and interpretation of modulatory studies of the UG.

Poster Ref: P3-D-019

Theme: D: Learning, Memory and Cognition

Contribution of the default mode network to global functional integration with increasing cognitive load.

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Introduction: The default mode network (DMN) comprises multisynaptic nodes that are considered to be connector hubs contributing to global integration of information. The interactions between the default mode and other large-scale brain networks have not been systematically assessed in a paradigm with parametric increase in cognitive load using fMRI. The aim of this study was to investigate the contribution of DMN to the global functional integration in a working memory task.

Methods: A group of 22 healthy adults (19-57 years old, mean = 35.0, SD = 11.2) were scanned during a block designed N-Back paradigm ranging in difficulty from 0 to 3-Back (including fixation) (Siemens Trio 3T scanner, 160 volumes, TR = 2s). Following a standard preprocessing pipeline, for each task block, weighted and undirected bivariate correlation matrices of 264 brain regions, corresponding to 14 large-scale brain networks (Power *et al.*, 2011), were clustered into modules using an Infomax community detection algorithm. The resulting information was visualised using circular and alluvial representations to assess changes in the modular functional brain connectivity architecture.

Results: The results suggest that the brain network modularity decreases with increasing task difficulty ($P < 0.05$). Although the overall network structure for all known large-scale brain networks remained intact at each task block, between fixation and 3-Back conditions 17% of the 58 DMN regions showed high flexibility, changing allegiance to the community that is commonly referred to as the task positive, fronto-parietal control network.

Conclusions: Overall, our findings indicate that the global functional integration in the brain increases with higher environmental demands, largely driven by the flexible DMN nodes. Such evidence provides support for a potential role played by the DMN in cognitive processing, which may have important implications for our understanding of brain function.

References: Power, J. D., Cohen, A. L., Nelson, S. M., Wig, G. S., Barnes, K. A., Church, J. A., . . . Petersen, S. E. (2011). Functional network organization of the human brain. Neuron, 72(4), 665-678. doi: 10.1016/j.neuron.2011.09.006

Poster Ref: P3-D-020

Theme: D: Learning, Memory and Cognition

Learning oculomotor behaviours: Cerebellar-driven sequence learning in normal populations.

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Introduction: Rehearsal of information in working memory is accompanied by prefrontal cortex (PFC) activity sustained across memory delays[1]. Improved working memory performance may be supported by systems engaged in automating cognitive operations. It has been proposed that parts of the cerebellar cortex (lobule HVIIa) that connect with the prefrontal cortex may be engaged in this process[2]. Trial-to-trial decreases in cerebellar activity reflect the process of cerebellar plasticity and may play important roles in the acquisition of cognitive skills[3]. We tested for changes in cerebellar activity related to improved performance of oculomotor sequences associated with rehearsal in working memory.

Methods: We tested the role of PFC and cerebellar circuitry during sequence acquisition under visual guidance and rehearsal in working memory. Human subjects (N=16) were scanned using functional MRI while they learned a spatial sequence (PRESENTATION), and then rehearsed it in working memory without visual cues (REHEARSAL). Sequences were repeated frequently (HIGH LEARNING) or infrequently (LOW LEARNING) and were presented and rehearsed in blocks of 1, 2 or 3 repetitions randomly. Analysis: PRESENTATION and REHEARSAL blocks were modelled separately. Eye movements were tracked during fMRI. Analyses presented relate to REHEARSAL.

Results: Provisional results show accuracy was significantly higher in HIGH than LOW learning and increased with each extra repetition in LOW. The interaction was significant: Accuracy rates in HIGH were at ceiling level throughout, whereas they increased with repetition in LOW. Activity time-locked to all blocks was found in circuitry known to support oculomotor control, including the frontal eye fields. As hypothesised, activity decreased faster when there was greater behavioural change in cerebellar areas including HVIIa (SVC, $p<0.001$).

Conclusions: These results are consistent with previous findings that cerebellar plasticity is characterised by decreasing cerebellar activity during cognitive learning, including in the oculomotor domain.

References:

[1]Miller, E.K., *et al.* (1996). J Neurosci, 16(16),5154-5167

[2]Ramnani, N. (2006), Nat Rev Neurosci, 7(7)511-22

[3]Balsters, J. H., & Ramnani, N. (2010). J Neurosci, 31(6),2305-2312

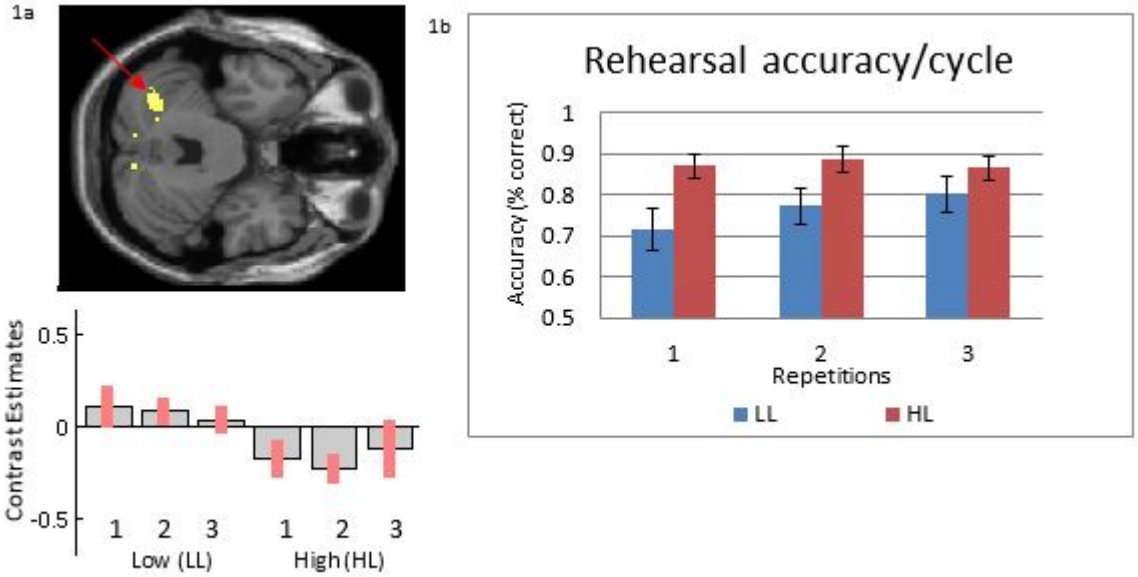

Figure 1a: Activation in cerebellar cortical lobule HVIIa. Differential rates of decreasing activity between high and low learning (1, 2 or 3 repetitions). Activity superimposed on the MNI canonical brain. Figure 1b: Accuracy showed a sig. interaction between learning and repetitions (means: LL1 =0.71;LL2 =0.77;LL3 =0.80;HL1 =0.87;HL2 =0.88;HL3 =0.87) $F=5.40$, $p<.05$. Error bars: +1/-1 SEM.

Poster Ref: P3-D-021

Theme: D: Learning, Memory and Cognition

The relationship between fornix microstructure and cognition in ageing and MCI.

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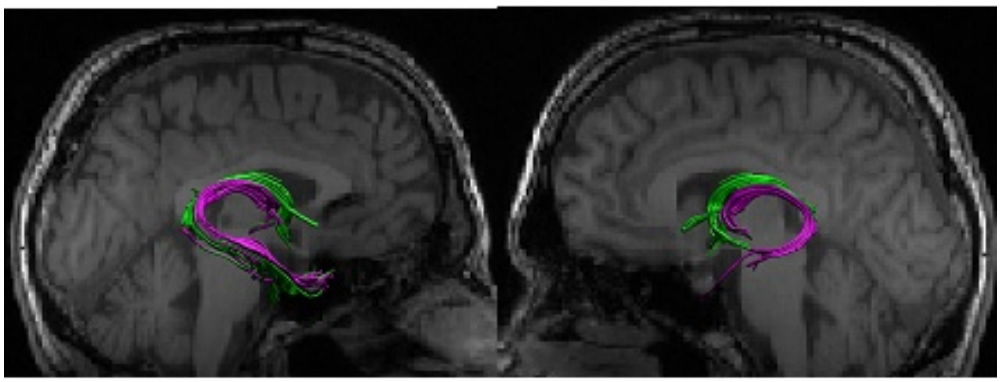
Research on the fornix to date, particularly in human populations, has typically treated this structure as a unitary tract. In fact, the fornix can be divided into two pathways (pre-commissural and post-commissural) each with different connections. While it is known that the fornix is crucial for memory processes, few studies have investigated the functional consequences of this pre:post commissural division. In the few animal studies, mixed results have occurred. The present experiment considered the functional relevance of these fornix tracts in a healthy aging population and in those with Mild Cognitive Impairment. The latter group are of particular interest because they show a loss of episodic memory and a breakdown of fornix microstructure. Diffusion weighted MRI was used, whereby a standardised ROI approach was performed with deterministic tractography. Micro and macrostructural values such as fractional anisotropy, radial diffusivity and tissue volume fraction were collected. Cognitive measures were derived from episodic memory and executive function tasks. The results in the healthy aging group showed a difference between pre- and post-commissural fornix function, with more episodic memory correlations in the post-commissural fornix. A particularly interesting finding came from the macrostructural differences between groups, where the post-commissural but not pre-commissural fornix revealed lower tissue volume fraction in the MCI group than in the control group. The results are considered in terms of our current understanding of how different hippocampal connections relate to memory and other aspects of cognition.



Pre-commissural and post-commissural fornix reconstructions in a healthy aging participant (pre-commissural in green and post-commissural in pink)

Poster Ref: P3-D-022

Theme: D: Learning, Memory and Cognition

Developmental exposure to different pesticides impairs spatial learning in male but not in female rats.

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Principe Felipe Research Center

Although pesticides are beneficial in controlling the proliferation of pests, they may have adverse effects in humans. The potential impact on humans of all pesticides used has not been established. Exposure to some pesticides during pregnancy and lactation may lead to cognitive impairment and motor disorders in children by mechanisms which remain unknown.

Aims: (1) To assess whether developmental exposure to the different types of pesticides: endosulfan, carbaryl and chlorpyrifos, affect spatial learning. (2) To assess if the effects are different in males and females.

Methods: Wistar rats were exposed to the three pesticides during their development (pregnancy and lactation) period. Spatial learning was tested using radial and morris water maze (MWM). Escape latency was measured in MWM. The ability to learn a radial maze was measured with a learning index: the difference between success and reference errors.

Results: The ability to learn the radial or MWM was not affected in females exposed to the pesticides. However, spatial learning was impaired in males. The escape latency was significantly increased in males exposed to endosulfan, carbaryl or chlorpyrifos. Learning index in radial maze was also reduced in males exposed to endosulfan and chlorpyrifos, but not to carbaryl.

Conclusion: Developmental exposure to these three pesticides induce gender-differential effects on spatial learning.

Poster Ref: P3-D-023

Theme: D: Learning, Memory and Cognition

Don't make me angry: Manipulating volitional choices to act or inhibit by subliminal emotional faces.

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Intentional choices to execute or inhibit one's own actions are a vital aspect of human conscious experience. Can such choices be influenced by subjectively invisible emotional stimuli? Typically, late-breaking forms of inhibitory control, occurring at the very final stages of voluntary action, have been thought to require conscious effort and awareness. We have previously shown that subliminal arrow stimuli that are explicitly associated with 'Go' or 'NoGo' responses can affect the conscious, intentional choice to act or inhibit one's own actions. Here, we show that intentional self-control can also be non-consciously manipulated by naturalistic, emotional stimuli that, importantly, are not explicitly associated with action or inhibition responses within the experiment. In a modified Go/NoGo task, participants responded to frequent green circles with a speeded button press (Reactive Go). Rare red circles indicated the response should be withheld (Reactive NoGo). Yellow circles indicated participants should make a quick, spontaneous decision whether to execute or withhold the prepotent button press (Intentional Go/NoGo). Crucially, prior to targets we presented backwards-masked subliminal faces, which had either angry or emotionally neutral expressions. EEG was recorded. Intriguingly, whilst primes had no effects on response times (neither Reactive nor Intentional), angry face-primes reduced the rate of choosing to act, compared to neutral primes. Moreover, EEG showed that angry primes modulated theta band activity in fronto-central areas, which has been associated with cognitive control. Our results elucidate an important new channel by which briefly seen or invisible emotional stimuli can modulate apparently volitional behaviour.

Poster Ref: P3-D-025

Theme: D: Learning, Memory and Cognition

Investigating the role of perirhinal histone deacetylase 2 in rodent object recognition memory.

Anna Smith, Helen Scott, Gareth Barker, James Uney and E. Clea Warburton

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Evidence suggests that histone deacetylases (HDACs), which remove acetyl groups from histone tails, act to suppress memory *in vivo* by regulating the transcription of memory-related genes (Guan *et al.*, 2009). HDAC2 is of particular interest as it is expressed in regions of the brain particularly associated with memory and has been found to be upregulated in Alzheimer's disease (AD) patients and mouse models of AD (Graff *et al.*, 2012). This study used viral vectors to investigate the role of HDAC2 in rat recognition memory as specific HDAC family subtypes can be targeted selectively using small hairpin RNAs (shRNAs). A lentiviral vector expressing a shRNA targeting HDAC2 (lenti-shHDAC2-CMV-EGFP) and a scrambled control vector (lenti-shSCR-CMV-EGFP) were produced. Lenti-shHDAC2-CMV-EGFP caused significant knockdown of HDAC2 protein expression in primary neuronal culture. 20 adult male Lister Hooded rats received bilateral infusions of either lenti-shHDAC2-CMV-EGFP (shHDAC2 group, n=10) or lenti-shSCR-CMV-EGFP (shSCR control group, n=10) into the perirhinal cortex (PRH).After recovery single item recognition memory was tested using a novel object preference task. Animals were allowed to freely explore a Y-maze containing an identical copy of an object in each of its distal arms for either a standard (maximum 40s exploration in 240s) or subthreshold (maximum 20s of exploration in 120s) amount of time. After a delay of 24 hours animals were returned to the arena, which now contained a third copy of the object seen previously (familiar object) along with a novel object, and allowed to explore for 180s. A discrimination ratio was calculated using the formula (novel object exploration-familiar object exploration)/total exploration. No significant effect of sample phase or treatment on discrimination ratio was observed. Additional subthreshold sample phases were then tested: 10s in 60s and 15s in 120s. Overall, no significant differences were seen between shSCR and shHDAC2 groups, suggesting that perirhinal HDAC2 may not play a role in long term object recognition memory.

Poster Ref: P3-D-026

Theme: D: Learning, Memory and Cognition

Subclinical checking tendencies and its relation to sense of agency.

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Sense of agency (SoA) refers to the subjective experience of controlling one's own actions and resultant effects. Recent research has indicated possible underlying SoA abnormalities in people with Obsessive Compulsive Disorder (OCD), although these findings are inconsistent. This study attempted to clarify the nature of SoA alterations for people with subclinical checking tendencies compared with non-checking controls. This was achieved by measuring both explicit and implicit aspects of the SoA in two separate tasks. In a 'Judgement of Agency' task, participants first engaged in a learning phase in which associations between actions (button press) and effect (tone type) were established. In the subsequent testing phase, the tone following the action was congruent or incongruent with participants' learned expectations and the participant's task was to rate their SoA. The checking group (n = 20) showed significantly higher agency judgements than the non-checking group (n = 22), indicating a greater explicit sense of agency. The second task required participants to estimate the time for their actions and resultant effects, which provided a measurement for the subjective temporal compression of the interval between an action and effect, i.e. intentional binding, which is recognised as an implicit measure of SoA. Intentional binding was stronger for checkers (n = 22) compared with non-checkers (n = 23). Together, these findings indicate that subclinical checkers experience greater explicit and implicit SoA compared with non-checkers. This could be related to their feeling of incompleteness, enhanced sense for responsibility, and it could have potential implications for clinical practice.

Poster Ref: P3-D-027

Theme: D: Learning, Memory and Cognition

Age related cognitive changes in the ability to monitor spatio-temporal patterns in a touchscreen foraging task.

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Foraging behaviour has been found to change in relation to ageing in animals and humans. In humans, foraging skills are often assessed using controlled experimental paradigms with a limited resemblance to natural foraging settings. Nevertheless, it has recently been proposed that only ecologically valid tasks can be used to accurately characterise the cognitive profile of healthy ageing in humans. In the present study, age related cognitive change was assessed in a computerised foraging task derived directly from recent studies on primate foraging. The task required participants to monitor spatio-temporal patterns of resource availability in a search environment presented on a touchscreen. The performance of undergraduate students below the age of 35 was compared with that of participants over the age of 65. The Montreal Cognitive Assessment (MoCA) was used to ensure that any age related effect was not due to mild cognitive impairment in the older group. Results showed that younger participants were spontaneously able to monitor two spatio-temporal patterns and successfully predict the correct locations to search at the beginning of each trial. Older participants by contrast were impaired in their ability to detect such patterns. In fact, a significant difference emerged when the proportion of successful first searches in each trial was compared between the two groups. These results confirmed that foraging tasks are a promising tool for the detection of subtle aspects of cognitive decline in healthy ageing. The results are considered in relation to the benefits of assessing cognitive changes in ageing in ecologically relevant tasks.

Poster Ref: P3-D-028

Theme: D: Learning, Memory and Cognition

Pre-stimulus subsequent memory enhancements: The role of random fluctuations in attention.

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Emotional events are remembered better than non-emotional events - a phenomenon known as Emotion-enhanced memory (EEM). Recent research has suggested that anticipation is a factor that contributes to memory enhancement at a neural level. One theory, predicated on changes observed in pre-stimulus ERP activity, is that anticipation leads to preparation, which increases processing efficiency- which in turn facilitates memory encoding (Park and Rugg 2010; Galli, Wolpe *et al.* 2011). However, recent data reveal that this pre-stimulus ERP effect can also been observed where no opportunity for preparation exists (Yick, Buratto & Schaefer, Submitted). This led us to predict that memory related ERPs at the anticipatory phase might reflect the random fluctuation in attention rather than preparatory activity. In order to test this, we conducted an ERP experiment to measure the difference due to memory (Dm) effect during a pre-stimulus phase using a subsequent memory paradigm. The Dm effect distinguishes between subsequently remembered and forgotten items, thus providing an index of successful encoding. We employed a S1-S2 (Stimulus 1: Cues - Stimulus 2: Pictures) Cueing-Subsequent Memory Paradigm. Upper case letters (O, X, Z) served as cue stimuli (S1) for Informative-Neutral, Informative-Negative, and Non-Informative cue conditions respectively. Emotional and neutral images were used for S2. Participants were instructed to anticipate the valence of upcoming pictures in response to cues. Our findings revealed a negative-going frontally distributed Dm effect for Non-Informative as well as Informative-Neutral trials at 600-800ms and 1550-2300ms in a 3000ms pre-stimulus time-window. In other words, the Dm effect was observed even when individuals had no information about subsequent picture valence and thus, no opportunity to prepare. These data provide support for the random fluctuation explanation of pre-stimulus memory related activity.

References

Galli, G., N. Wolpe, *et al.* (2011). "Sex Differences in the Use of Anticipatory Brain Activity to Encode Emotional Events." The Journal of Neuroscience 31(34): 12364-12370.

Park, H. and M. D. Rugg (2010). "Prestimulus hippocampal activity predicts later recollection." Hippocampus 20(1): 24-28.

Poster Ref: P3-D-029

Theme: D: Learning, Memory and Cognition

Timing the availability of predictive signals: A cerebellar asymmetry for regulating word association priming.

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Bangor University

The acquisition of language is underpinned by neural mechanisms that enable learning of associations between sounds that are likely to occur in close temporal relation. A stimulus that activates the meaning of a word will facilitate processing of a semantically related item- semantic priming. Thus, priming is a predictive process that facilitates efficient speech production, comprehension and reading. Since discourse is temporally dynamic, the benefits of priming depend on timing the availability of predictive signals. If a primed word is activated too soon, it can compete with the word activating it, delaying access to the priming word or causing naming errors. These errors are particularly conspicuous in some aphasic patients with anomia who make frequent semantic parraphasic errors. Thus priming must be modulated by brain mechanisms that facilitate and inhibit it with a temporal precision needed for efficient language performance. Cerebellar circuitry provides a precise neural clock and has been implicated in predicting not only the sensory consequences of action, but predictive sentence processing. We tested whether these cerebellar predictions were supported by inhibitory and facilitory processes. In a mixed group design (n=41), automatic word association priming was measured in a lexical decision task before and after 40 seconds of continuous theta burst stimulation of the left or right cerebellum (1cm below inion, 3cm lateral), or a vertex control site. (Study recruitment criteria included that participant medical history did not contraindicate brain stimulation.) Left cerebellar stimulation decreased priming, whereas right cerebellar stimulation increased priming. The results support the proposal that the cerebellum contributes to facilitory and inhibitory processes that dynamically regulate word priming.

Poster Ref: P3-D-030

Theme: D: Learning, Memory and Cognition

Hippocampal theta during memory guided virtual navigation in human intracranial EEG.

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Theta frequency oscillations are prominent in the rodent hippocampal local field potential during movement, and are typically in the range of 6-10Hz. Theta oscillations are also associated with human spatial memory function, typically in the range of 3-7Hz. However, the exact relationship between human theta oscillations, movement and spatial memory function is currently unclear. We examined intracranial EEG recordings from depth electrodes located in the hippocampi of twelve pre-surgical epilepsy patients performing a self-paced virtual reality navigation and spatial memory task. In this task, participants were asked to navigate towards, and encode the location of, various visible objects within a single environment. Participants were subsequently cued with the image of a single object, then placed back in the environment and asked to navigate to the remembered location of that object.

We found that power in the higher frequency (6-10Hz) theta band increased significantly during a 1s period around virtual movement onset compared to 1s stationary periods, consistent with MEG findings in a similar task (Kaplan *et al.*, 2012). Moreover, 6-10Hz theta power during this 1s movement onset period correlated with subsequent memory performance. An increase in lower frequency (3-6Hz) theta power was also observed around movement onset, but did not reach significance, and did not correlate with subsequent memory performance. Next, we identified a more sustained increase in broadband ~3-16Hz oscillatory power during the 3s cue period, but only 6-10Hz theta power during this 3s period correlated with subsequent memory performance. These findings suggest that human hippocampal theta oscillations in the higher (6-10Hz) band are associated with both virtual movement and the accuracy of spatial memory function.

Acknowledgements: this work was supported by the MRC, Wellcome Trust, and the Department of Health's NIHR UCLH/UCL Biomedical Research Centre

Kaplan R, Doeller CF, Barnes GR, Litvak V, Duzel E, Bandettini PA, Burgess N (2012) Movement-related theta rhythm in humans: coordinating self-directed hippocampal learning. PLoS Biology e1001267.

Poster Ref: P3-D-031

Theme: D: Learning, Memory and Cognition

Implicit indicators of national identity modulate brain activation when processing empathy for in-group and out-group members in pain.

Katie Nicol[1], Joshua Skewes[2], Adam Moore[3], Kenneth M. Prkachin[4], Neil Roberts[5], Andreas Roepstorff[2] and Laura Cram[6]

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We use functional magnetic resonance imaging (fMRI) to investigate the effects of overt and covert nationality cues on empathy for the pain of others. 27 healthy participants from Scotland completed an fMRI scan, Empathy Quotient (EQ) questionnaire and a questionnaire to quantify attachment to Scotland (national attachment). During the fMRI sequence, participants viewed videos of people experiencing shoulder pain and rated pain intensity and unpleasantness. Each video showed someone of the same (Scottish) or different (English) nationality. Videos were previously classified as either high or low pain. In addition, half of the trials were preceded by an implicit prime of the Scottish flag. High *vs* low pain videos resulted in greater activation in right insula ($p<0.001$), right cerebellum ($p<0.001$), left superior frontal gyrus (SFG) ($p=0.001$) and left inferior frontal gyrus ($p=0.003$) when controlling for empathy and national attachment. EQ score positively correlated with activation in the precuneus ($p<0.001$) in response to high pain *vs* low pain videos. Videos showing people of the same nationality (Scottish) that included the flag prime elicited greater haemodynamic response in right SFG ($p<0.001$) than videos showing the same nationality without a flag prime, controlling for empathy and attachment. Increased activation was found in right anterior cingulate cortex (ACC) ($p=0.012$) with small volume correction (SVC). EQ score correlated positively with activation in fusiform gyrus ($p<0.001$) within the contrast of same nationality with flag *vs* without flag. There was a positive correlation between attachment and activation in posterior cingulate cortex ($p=0.005$), when viewing people of a different nationality (English) with no flag prime compared to when a national flag prime was present. There was no significant difference in activation between viewing videos of people of either explicit nationality, in the absence of the national flag prime. The presence of a national flag, even when presented implicitly, has an effect on the way in which we process empathy for others in pain. So the judgments that we make about others may be modulated without our conscious knowledge. This has implications for clinical practice and in political and policy-making settings.

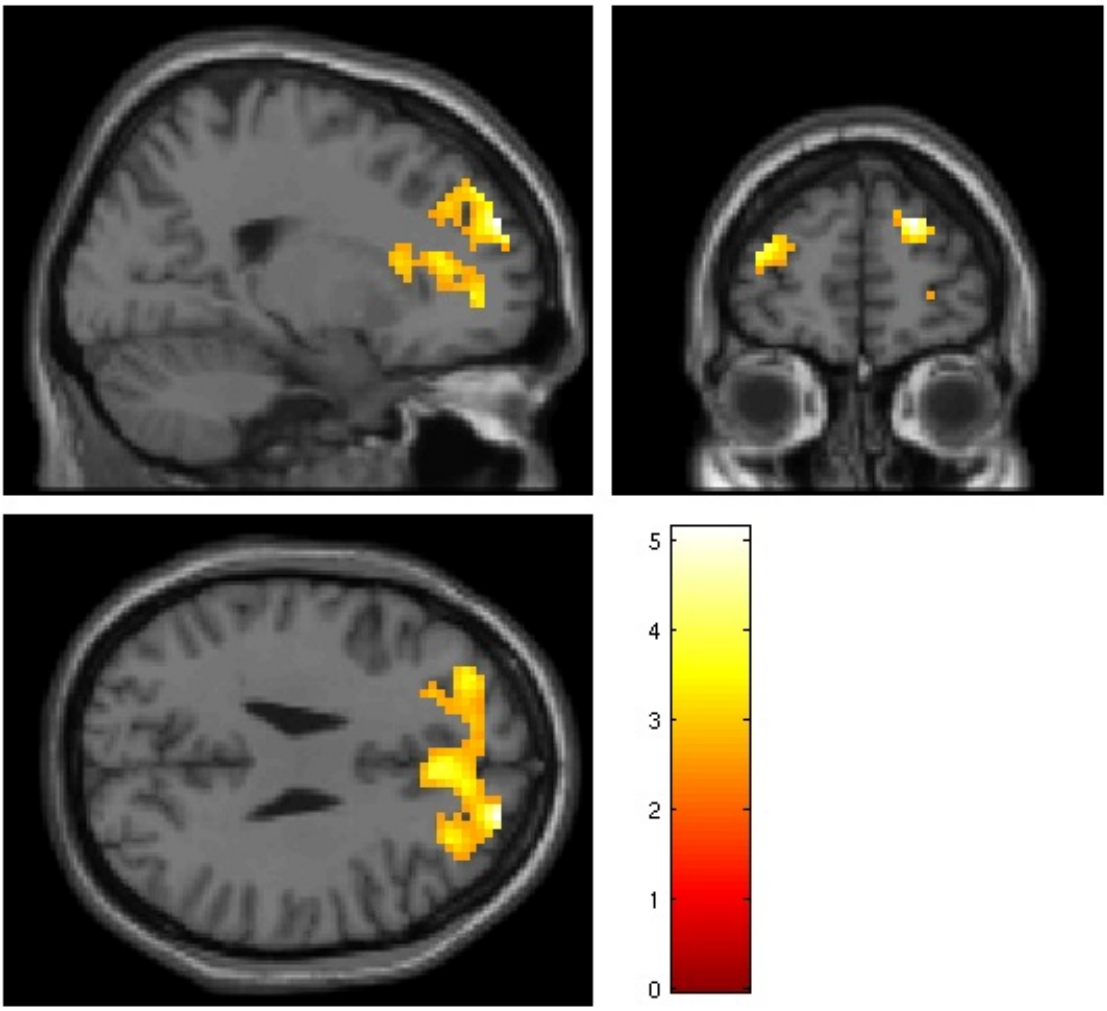

Figure 1. Controlling for EQ and attachment scores, peak activity is found in the right SFG when exposed to the flag prime versus no prime when viewing someone of the 'same' nationality (Scottish). After small volume correction, activity is also seen in the right ACC.

Poster Ref: P3-D-032

Theme: D: Learning, Memory and Cognition

Implicit nationality primes modulate brain activation when processing another person's experience of pain.

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Nationality is a real world marker of group identity. We explore the effect of implicit nationality primes on empathy for others in pain, using functional magnetic resonance imaging (fMRI). 25 Danish participants completed an MRI scan and 40 item Empathy Quotient (EQ) questionnaire. During the fMRI sequence, participants viewed a series of videos of individuals experiencing shoulder pain and were asked to rate both pain intensity and pain unpleasantness. Individuals in each video were either the same nationality as participants (Danish) or a different nationality (German). Videos were classified using the facial action coding system as either "high pain" or "low pain". An implicit prime was also displayed, which was either the participants' national flag (Danish flag) or no flag. Controlling for individual differences in empathising at the trait level, significantly greater activation in response to high pain compared to low pain videos was observed in the bilateral inferior frontal gyrus ($p<0.001$), left middle temporal gyrus ($p<0.001$), right pyramis ($p=0.001$) and left superior frontal gyrus ($p=0.002$). A main effect of prime (flag/no flag) was also observed in left superior parietal lobe ($p=0.004$) (figure1), and a trend towards significance in two large clusters within right insula ($p=0.071$, $p=0.118$) following small volume correction (SVC). A positive nationality x prime interaction was evident in left middle temporal gyrus ($p<0.001$) and left culmen ($p=0.001$). All p values reported at a threshold of 0.005 and FWE corrected. We observe a significant effect of prime, such that presence of an implicit national flag was associated with increased activation in superior parietal lobe, and a trend towards significant activation in the insula, both of which are known to be involved in the processing of empathy for pain. Furthermore, our results show that as activation in response to nationality increased, so did activation in response to national flag in the culmen and middle temporal gyrus, which have previously both been found to show increases in activation in response to viewing others in pain. We have, for the first time, provided biological evidence for the arousing effects of national flags, and have demonstrated that such cues affect how we perceive others.

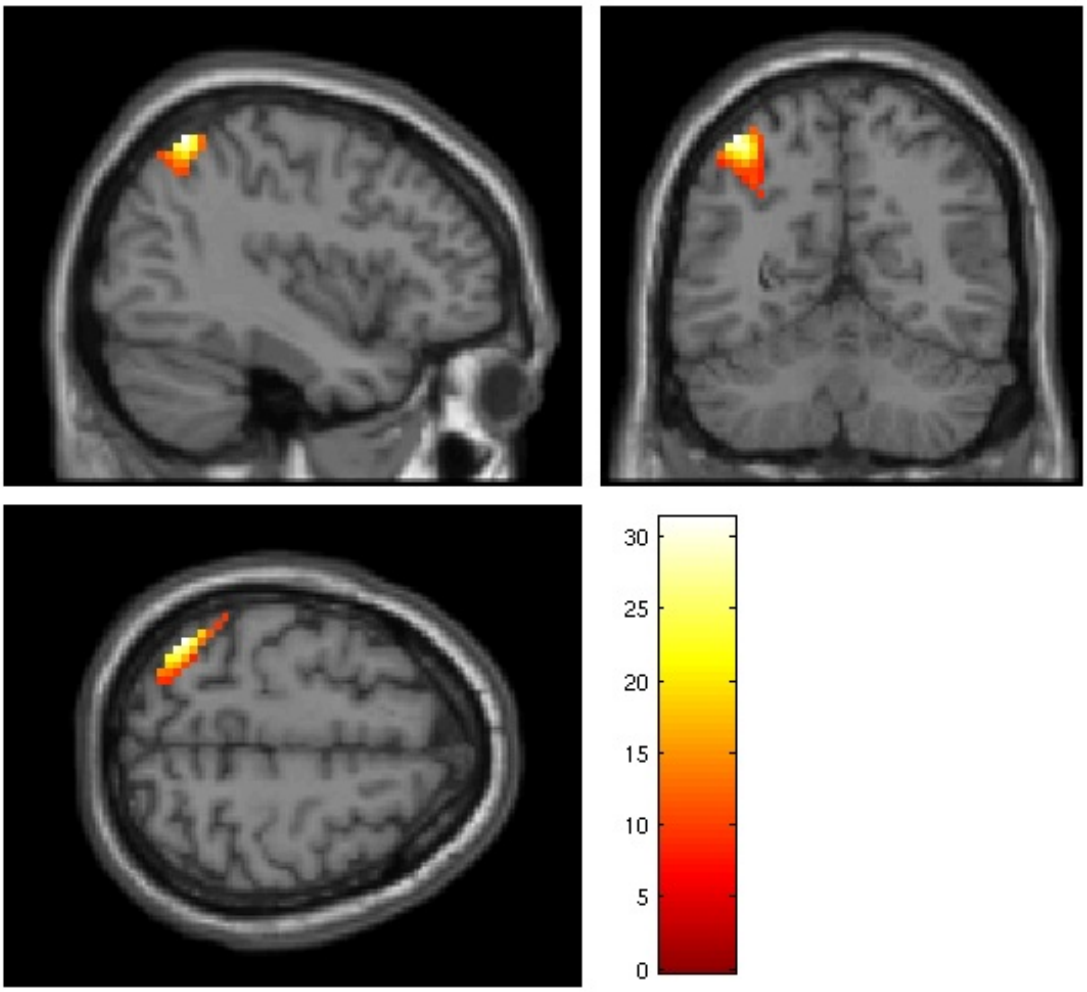

Figure 1. Main effect of implicit prime (flag/no flag) in the left superior parietal lobe.

Poster Ref: P3-D-033

Theme: D: Learning, Memory and Cognition

EEG correlates of contingency judgments in a streamed-trial procedure.

Noelia Do Carmo Blanco, Angèle Brunellière and Jeremie Jozefowiez

Université de Lille, France

Associative learning is the ability of detecting statistical regularities in the environment, allowing the expectation of one stimulus (the outcome) on the basis of another (the cue). This faculty has a basic role in cognition. This study investigates EEG correlates of that fundamental form of learning.

Participants were exposed to rapid flows of 100-ms stimuli (cue and/or outcome sequences). At the end of a flow, they had to judge whether the outcome was contingent upon the cue, that is to say, whether the outcome was more likely following presentation of the cue than omission of it. We manipulated the frequency of the outcome in the presence vs. the absence of the cue, creating 3 types of stimulus flow: negatively contingent (the outcome was slightly less likely following the cue), null (the outcome was just as likely following the cue than following its absence), and positively contingent (the outcome was slightly more likely following the cue).

At the behavioural level, we found that contingency judgments varied accordingly with the type of flow (higher probability to perceive a cue-outcome relation in positive flows compared to null ones and null flows compared to negative ones). At the EEG level, we found that processing of the cue-outcome sequence in the null condition lead to an increased event related potentials (ERP) amplitude compared to the negative and the positive condition.

These finding could be explained in terms of predictive coding, where neural signals are related to internal predictions and goals rather than exclusively to stimulus. This indicates a comparison between expected and actual visual input, as a result of previous information to the system.

Poster Ref: P3-D-034

Theme: D: Learning, Memory and Cognition

Effective connectivity from early visual cortex to posterior occipito-temporal face areas predicts developmental prosopagnosia.

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Face processing is mediated by interaction of several functional areas within the human brain. The fusiform face area (FFA) and anterior temporal lobe (ATL) have been related to recognition of facial identity. In two previous studies (Garrido *et al.*, 2009; Furl *et al.*, 2011) individuals with a lifelong face recognition impairment, called developmental prosopagnosia (DP), showed structural and functional neuronal alterations in these areas. The present paper investigated how face selectivity arises, and how brain alterations associated with this face recognition impairment arise as a function of network connectivity.

Using functional magnetic resonance imaging and dynamic causal modelling, we investigated how effective connectivity was affected in DP compared to a control sample by assessing dynamic causal connectivity models of a network which includes regions showing stronger blood oxygen level dependency (BOLD) response to faces compared to objects (ie. face selective regions).

Results showed that a feedforward architecture from early visual cortex (EVC) to FFA and posterior superior temporal sulcus (pSTS) best explained how face selectivity arises. Although this was the case for both the control sample and DP, the strength of the feedforward connectivity carrying facial information from EVC to FFA and STS were reduced in DP. These altered network dynamics in DP account for the diminished face selectivity in regions previously reported to be affected in DP (Furl *et al.*, 2011).

This empirical finding suggests a novel view on the relevance of feedforward projection from EVC to FFA and STS in generating cortical face selectivity and individual differences in face recognition ability.

Poster Ref: P3-D-035

Theme: D: Learning, Memory and Cognition

Local projections of the medial entorhinal cortex layer 2 stellate and pyramidal cells to the deep MEC layers.

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The medial entorhinal cortex (MEC) is a 6 layer structure containing cells with various spatial firing properties, including grid, head direction and border cells. superficial and deep layers of the MEC differ functionally and anatomically such that the most superficial cell layer, layer 2 (L2) is where the majority of cells with grid firing properties are located whereas the deeper layers house cells with head direction modulated activity. While principal neurons in L2 send long-range projections to the hippocampal dentate gyrus and CA1, and make local connections within L2, connections from L2 to deeper layers of MEC have not systematically studied. This is partly due to a lack of unambiguous delineation of the deep MEC layers. Here we show that the deep layers Layer 5a and 5b can be marked by expression of two transcription factors Etv-1 and Ctip2 as well as by extrahippocampal and local projection profiles. We studied the information flow from L2 to the principal cells of the deep layers using stellate and pyramidal cell specific Cre driver mouse lines. Investigation of the distribution of synaptic terminals of the two cell populations by expressing GFP tagged synaptophysin revealed that stellate cells have abundant projections to deep layers whereas pyramidal cell terminals were scarce. Taking advantage of the layer specific expression of Etv-1 and Ctip2 we showed that terminals of stellate cells were localized in Layer 5b and L4, but not in L3 and L5a. In agreement with the anatomical data, optogenetic activation of L2 stellate cells combined with patch clamp recordings from deep layers revealed inputs onto L5b neurons and to a large extent a lack of projections to neurons in L3 and L5a. Together our data reveals a previously unknown cell type and layer specific information flow within the MEC from stellate cells to L5b neurons. Remarkably this information is not shared with neurons in L5a which provide the major MEC projections outside of the hippocampus.

Poster Ref: P3-D-036

Theme: D: Learning, Memory and Cognition

Sleepiness moderates the effect of L-DOPA on the arbitration between goal-directed and habitual control.

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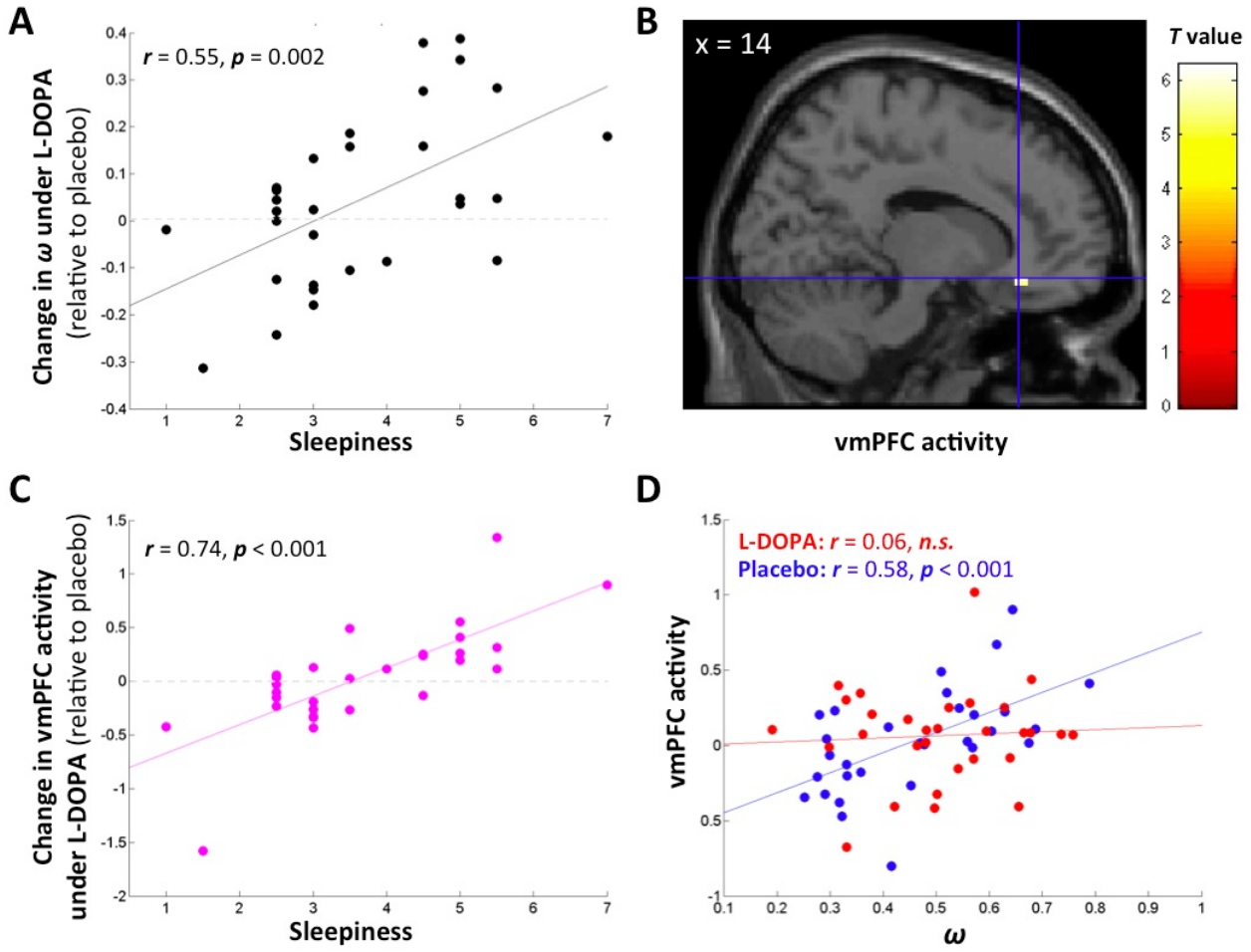
Increasing dopamine levels seem to promote goal-directed control over habitual control of choice behaviour [1], but what happens when we are sleepy? Executive functioning impairments following sleep loss involve the dopamine (DA) system [2, 3], thus sleepiness could reflect compromised DA functioning. Cools and D'Esposito [4] proposed that endogenous DA levels might moderate the effects of dopaminergic manipulation. Here, we investigated if sleepiness moderates the effect of L-DOPA on the arbitration between goal-directed and habitual control.

Thirty healthy participants from this ongoing study were included in this analysis. Each participant had two visits. At each visit, they took the medication (L-DOPA/placebo) and completed the Karolinska Sleepiness Questionnaire (KSS; German version, [5]). They then did a modified two-stage decision task [6,7] in the fMRI scanner. Using model fitting as reported previously [7], we estimated ω, the degree of goal-directed over habitual control for each individual per visit. Sleepiness was the average of KSS scores across visits. First level statistics of fMRI data were set up as detailed in [6], where parameter estimates for the first regressor represented brain activity associated with the main effect of task.

We found that effect of L-DOPA on ω depended on sleepiness, $F(1,28) = 12.4$, $p = .002$. L-DOPA increased ω in sleepy individuals, but decreased that of awake individuals (Fig. A). We found a positive interaction between drug condition and sleepiness on vmPFC activity (Fig. B). L-DOPA augmented vmPFC activity in sleepy individuals, but reduced that of awake individuals (Fig. C). vmPFC activity was positively correlated with ω under placebo, but not under L-DOPA (Fig. D).

We conclude that our observations are in line with "the inverted u-shape hypothesis" [4], where sleepy individuals with less DA benefited from L-DOPA while awake individuals were impaired due to a DA overdose. Future studies should clarify the relationship between trait-like vulnerabilities to sleep loss [8] and endogenous DA levels.

1. Wunderlich *et al.*, 2012 2. Volkow *et al.* 2012 3. Han, *et al.*, 2014. 4. Cools and D'Esposito, 2011 5. Åkerstedt *et al.*, 1996 6. Daw *et al.* 2011 7. Schad *et al.*, 2014. 8. Van Dongen *et al.*, 2004



A) Relationship between sleepiness and change in ω. B) Positive interaction between drug condition and sleepiness on vmPFC activity (neural correlates of stage 2 choices and outcome onsets; p < 0.05, FWE cor.). C) Relationship between sleepiness and change in vmPFC activity. D) Relationship between vmPFC activity and behaviour in placebo condition, but not in L-DOPA.

Poster Ref: P3-D-037

Theme: D: Learning, Memory and Cognition

Neural representation of space by place and grid cells on the vertical plane in rats.

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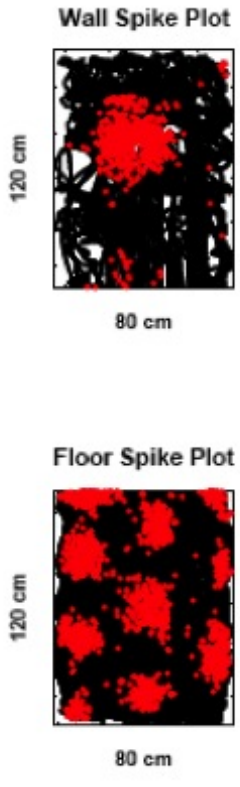
Institute of Behavioural Neuroscience, University College London

Place cells (PCs) are hippocampal neurons whose firing dramatically increases every time an animal exploring an environment traverses one particular region of it, producing a focus of activity known as a place field. Similarly, grid cells (GCs), neurons found one synapse upstream in entorhinal cortex, display multiple evenly spaced place fields, arranged in a hexagonal array tessellating the whole space. Therefore, in contrast to PCs encoding the animal's actual location, GCs process metrics by determining travelled distances, information required for successful navigation. Many studies have focused on PCs and GCs in horizontal environments, but little is known about their spatial encoding of the vertical domain. This study addressed this matter by testing the hypothesis that both these classes of neurons would maintain their spatially-modulated firing as the animal moves onto a vertical wall. Our preliminary results show that whilst PCs display very similar firing on the wall, GCs exhibit a substantial reduction of the number of place fields along with a dramatic increase of the inter-field distances and a breakdown of the hexagonal pattern. These results suggest that GCs' ability to process distances is radically impaired in the vertical domain, and that the neural representation of space is thus different for vertical space than for horizontal.



Spiking activity exhibited by a single grid cell (red) as the animal moves (black) between an horizontal surface (bottom row) and vertical wall (top row). Our preliminary results suggest that grid cells on the vertical plane form a pattern of activity which strongly diverged from the representation observed on horizontal plane and that the z-dimension is quantitatively different than horizontal.

Poster Ref: P3-D-038

Theme: D: Learning, Memory and Cognition

Facial expression processing in neuronal nets: Influences of digital image filtration of the face pattern and visual attention-related aspects of nonverbal communication

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The well-known face bar code using predominantly horizontal spatial frequency filtration mimics the work of only some primary visual cortex neurons (Dakin, Watt, 2009). In addition we found that diagonal components of the spatial frequency spectrum are also important for face perception. They contain individual characteristics and reflect emotional states of human face. Dynamic scene filtration was presented earlier (Logunova *et al.*, 2014). Wavelet filtration successfully achieves isolated face properties that are significant for an observer permitting the use of only 20% of the wavelet distribution for recognition. This incomplete half-tone version is reminiscent of incomplete contour testing and data (Foreman, Hemmings, 1987). Depending on what features of the face are being perceived visual system dynamically switches the processing from one of the visible portions of the spatial frequency band of the spectrum to another. This process in real life is mostly unconscious but represents a crucial step for subsequent decision-making. We used fMRI to study the neural nets participating in face processing and decision- making depending on the feature properties of the face. Changing instructions switches observer's attention from one feature to another. We revealed patterns of neuronal activation caused by different instructions, using a stable set of face images. Brain activation patterns in our experiments were reflected in earlier research of non-verbal communication and most patterns contain 'mirror neurons'. The brain structures providing decisions in non-verbal information space (maybe in verbal space as well) have functionally opponent relationships one against another. To make correct decisions about what is physically the same object, different brain areas can be involved according to the instructions given to the participant.

Supported by RSCF14-15-00918; RSCF 14-18-02135.

Poster Ref: P3-D-039

Theme: D: Learning, Memory and Cognition

The effect of psilocybin on frontoparietal effective connectivity: Insights from DCM for fMRI and MEG.

Mendel Kaelen[1], Bernadette van Wijk[2], Rosalyn Moran[3], Suresh Mutukumaraswamy[4], Joshua Kahan[2], Andre Ribeiro[1], Leor Roseman[1], Csaba Orban[1], David Nutt[1] and Robin Carhart-Harris[1]

[1]Imperial College London, [2]University College London, [3]Virginia Tech Carilion Research Institute, USA, [4]University of Auckland, New Zealand

Psilocybin is a classic psychedelic drug that produces marked psychological effects *via* agonist actions on serotonin 2A receptors. The idiosyncratic nature of these effects, make psychedelics important tools for the study of consciousness. Recent studies revealed broadband desynchronization and reduced functional connectivity within the default mode network after intravenous psilocybin in healthy volunteers. In the present study we used dynamic causal modelling (DCM) for magnetoencephalography (MEG) and functional magnetic resonance imaging (fMRI) to ask how these changes are mediated at the level of effective connectivity. Two nodes were chosen for the DCM analysis, based on their known interconnectivity and sensitivity to psilocybin: The medial prefrontal cortex (mPFC) and the posterior cingulate cortex (PCC). Effective connectivity of the intrinsic and extrinsic connections of these nodes and its modulation by psilocybin was estimated. The results suggest a key role for psilocybin affecting spontaneous brain activity *via* increasing excitability of layer V pyramidal cells. This is consistent with the dense expression of serotonin-2A receptors on deep pyramidal neurons, as well as their prevalence in the PCC and the mPFC.

Poster Ref: P3-D-040

Theme: D: Learning, Memory and Cognition

Prediction of brain age suggests accelerated atrophy after traumatic brain injury.

James Cole, Robert Leech and David Sharp

Imperial College London

Objective: The long-term effects of traumatic brain injury (TBI) can resemble those observed in normal ageing, suggesting that TBI may accelerate the ageing process. We investigate this using a neuroimaging model that predicts brain age in healthy individuals and then apply it to TBI patients. We define individuals' differences in chronological and predicted structural 'brain age', and test whether TBI produces progressive atrophy and how this relates to cognitive function.

Methods: A predictive model of normal ageing was defined using machine learning in 1537 healthy individuals, based on MRI-derived estimates of grey matter (GM) and white matter (WM). This ageing model was then applied to test 99 TBI patients and 113 healthy controls to estimate 'brain age'.

Results: The initial model accurately predicted age in healthy individuals (r = 0.92). TBI brains were estimated to be 'older', with a mean predicted age difference (PAD) between chronological and estimated brain age of 4.66 years (± 10.8) for GM and 5.97 years (± 11.22) for WM. This PAD predicted cognitive impairment and correlated strongly with the time since TBI, indicating that brain tissue loss increases throughout the chronic post-injury phase.
Interpretation.

TBI patients' brains were estimated to be 'older' than their chronological age. This discrepancy increases with time since injury, suggesting that TBI accelerates the rate of brain atrophy. This may be an important factor in the increased susceptibility in TBI patients for dementia and other age-associated conditions, motivating further research into the 'age-like' effects of brain injury and other neurological diseases.

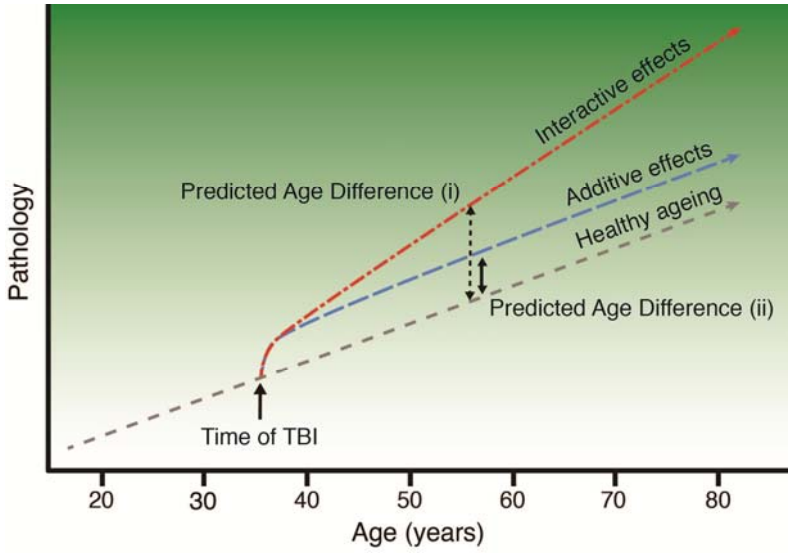

Figure 1. Model of premature brain ageing in traumatic brain injury
The grey line represents the trajectory of healthy ageing as age increases, against a background gradient of increasing susceptibility to age-related pathology. Occurrence of TBI is indicated (black arrow), with acute pathology causing an immediate departure from a healthy brain state.

Poster Ref: P3-D-041

Theme: D: Learning, Memory and Cognition

Cognitive performance validity test failure and psychological factors in mild cognitive impairment.

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Patients with MCI may or may not progress to dementia. In our clinical experience some patients fit the diagnostic criteria for MCI but secondary factors may account for their poor performance on cognitive tests. By using cognitive Performance Validity Tests (PVTs) we may be able to identify people who perform poorly on cognitive tests for reasons other than incipient dementia. Recent research has shown that 6-13% of people with MCI fail PVTs, and using their results in research creates unnecessary noise in the data (Rienstra *et al.*, 2013). We recruited 20 people diagnosed with MCI and 14 healthy controls (HC). The MCI patients completed 3 PVT tests (TOMM, WMT & DCT - comprising 9 PVT scores) and 3 questionnaires related to cognitive symptoms (CS), health anxiety (HA), somatic symptoms (SOM), depression (DEP), panic (PAN) and anxiety (ANX). The HCs completed the questionnaires. Results: 15% of our MCI sample failed at least 4 of 9 PVT scores; 20% failed at least 2 of 9 PVT scores. Selected TOMM scores were significantly correlated with a few measures of HA, CS and ANX, and the DCT was correlated with one HA measure, but the findings did not show robust relationships between PVT performance and psychological symptoms. The MCI group reported higher rates of current CS but there were no other differences between the MCI and HC groups on psychological questionnaires. Preliminary results indicated that PVT-fail patients had lower scores on the WMT clinical memory scores. Discussion: We replicated the finding that a proportion of people with MCI fail PVTs. Therefore, PVTs should be part of cognitive assessment in MCI research and caution should be used when interpreting the neuropsychological test results in persons who fail PVTs. The results provided only marginal support for our hypotheses regarding PVT failure and psychological factors in this group. There was no evidence that PVT failure was related to bias in CS reporting, but the sample size was too small for formal analysis. Further research is required to uncover the causes of PVT failure in this group and longitudinal follow-up will be crucial. In a future study we will examine how these PVT results relate to neurocognitive test results and clinical outcome (conversion to dementia or reversion to normal).

Poster Ref: P3-D-042

Theme: D: Learning, Memory and Cognition

Polygenic contribution of fragile X mental retardation protein targets on cognition in narrow and broad psychosis: The use of coding SNPs versus linkage disequilibrium (LD) pruning.

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Schizophrenia is a complex disorder including deficits in cognition, with multiple genes contributing to these deficits. In this study, we explored how a polygenic score generated from 832 FMRP (Fragile X Mental Retardation Protein) targets might influence cognitive performance in patients with psychosis, grouped into four modules. Of particular interest was the effect on association with cognition of two different ways of selecting SNPs for use: standard LD pruning versus the use of functional information. We used the WTCCC2 GWAS, including 298 narrow psychosis and 74 broad psychosis cases who had participated in a battery of cognitive tests. We found no significant association between FMRP polygenic scores within all FMRP targets or each of 4 modules when using standard LD pruning. However, the polygenic score comprised of coding SNPs from module 3 using a p-value threshold of less than 0.05 (21 SNPs) was strongly associated with the Vocabulary Test from the Wechsler Memory Scale (WMS-III) and verbal IQ in narrow psychosis cases($p = 5.9x10-7$, $R2 = 0.048$ and $p = 3.2x10-6$, $R2 = 0.040$). These findings were replicated in the independent broad psychosis sample ($p = 6.9x10-6$, $R2 = 0.13$ and $p = 0.016$, $R2 = 0.056$). Of these 21 SNPs, 9 were missense (42.9%) while the rest were synonymous. Results from the present study indicate that target genes of FMRP that are expressed constantly, irrespective of the stage of development, account for as much as 10% of verbal cognition. This study provides evidence promoting the selective use of SNPs in coding regions of the genome versus all the SNPs found in a given pathway.

Poster Ref: P3-D-043

Theme: D: Learning, Memory and Cognition

ERP signals of timing prediction error in aversive associative learning.

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In the literature, the importance of medial prefrontal cortex (mPFC) and its interactions with the dopaminergic system in learning and predicting events is clearly established. Mediofrontal event-related potential (ERP) components originating from mPFC, such as feedback-related negativity (fERN), have been found to code for Feedback Prediction Error during conflict detection and performance monitoring. Such fERN-like components are usually observed after unexpected feedback or unexpected omission of feedback. Evidence from single neuron and fMRI studies about predictive learning reported both mPFC and dopaminergic activity not only following violations of feedback expectancy, but also following violations of the expected timing of feedback (i.e., for expected feedbacks occurring with unexpected timing), thus also coding for a Timing Prediction Error (TPE). Nevertheless, to date, ERP components of TPE have never been directly investigated, and it is still unclear if this process relates to fERN-like components. The present study aimed at testing whether fRN-like components are associated with outcomes that occur with unexpected timing, even if the outcomes themselves are predicted. A Pavlovian aversive conditioning paradigm was used for this purpose, during which two visual stimuli were paired either with an aversive (shock) or with a neutral feedback, both unexpectedly shifted in time on 20% of trials. ERP analysis revealed stronger mediofrontal peak amplitudes for feedback occurring at unexpected times, as compared with expected times.

Poster Ref: P3-D-044

Theme: D: Learning, Memory and Cognition

The effect of noise on long-term memory encoding of students on a school environment.

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Society is becoming more conscious of the problems of 'noise pollution' on the environment therefore cognitive psychologists are gathering evidence to see if this has a disruptive effect on cognitive performance. However there is lack of unanimity on the effect of white noise in memory. Most studies focused on the effect of white noise on short-term memory consequently the literature on the effects of noise on long-term memory is not as vast or conclusive.
Bell *et al.* (1984) showed that noise present during initial exposure to the list of words reduces immediate recall of words under quiet conditions but if present during recall stage, it did not have any effect. Therefore he suggested that the negative effect on recall observed on previous research was dependent of the presence of noise during learning phase. This study tried to simulate the conditions in which students memorise information and means to determine if random noise has a disruptive effect on students' long-term memory. For this research sixty undergraduate students participate in two conditions (learning phase and recalling phase) were they were asked to memorise a short list of words which they would be asked to recall later. They were divided into four groups 15 of them would hear noise during the experiment while other 15 would not, this was the control. The rest was presented with noise either while memorising or recalling. The results show a significant decrease in the number of words recalled between the control and the recalling phase with noise. The other effects were not significant.

We have shown that random noise has an effect on undergraduates' long-term memory retrieval, but there is still more research needed in order to determine other effects of noise such as volume or the relation between memory span and noise

Adknowledgements

I would like to thank my module supervisor Kate Doran who gave me advice on the statistical analysis and my peer Alex Gibbson who suggested changes on the design of the experiment and helped collect the data.

References

Bell, P. A., Hess, S., Hill, E., Lee Kukas, S., Richards, R. W., & Sargent, D. (1984). Noise and context-dependent memory. Bulletin of the Psychonomic Society, 2(22), 99–100.

Poster Ref: P3-D-045

Theme: D: Learning, Memory and Cognition

Evidence for a spatial map in the rostral thalamus.

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Damage involving the anterior thalamic and adjacent rostral thalamic nuclei may result in a severe anterograde amnesia, similar to the amnesia resulting from damage to the hippocampal formation. Little is known, however, about the information represented in these nuclei. To redress this deficit, we recorded units in three rostral thalamic nuclei in freely-moving rats (the parataenial nucleus, the anteromedial nucleus and nucleus reuniens). We found units in these nuclei possessing previously unsuspected spatial properties. The various cell types show clear similarities to the place cells, head direction cells, and border cells described in hippocampal and parahippocampal regions. Based on their connectivity, it had been predicted that the anterior thalamic nuclei process information with high spatial and temporal resolution while the midline nuclei have more diffuse roles in attention and arousal. Our current findings strongly support the first prediction but directly challenge the second prediction. The rostral thalamic spatial cells described here may reflect direct hippocampal/parahippocampal inputs, a striking finding of itself, given the relative lack of place cells in other sites receiving direct hippocampal formation inputs. Alternatively, they may provide elemental thalamic spatial inputs to assist hippocampal spatial computations. Finally, they could represent a parallel spatial system in the brain.

Poster Ref: P3-D-046

Theme: D: Learning, Memory and Cognition

Neuronal representation of space and objects in rat anterior claustrum.

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Trinity College Dublin, Ireland

The claustrum of the mammalian brain is an anatomically-substantial but largely unexplored and uninvestigated structure. The claustrum has been the subject of a limited degree of speculation regarding its potential functions, however, its physiological role still remains unknown. In the present study, we investigated the spatial and temporal properties of neurons located in the anterior claustrum in freely-moving rats. Extracellular recordings were performed using 32-channel drivable microelectrode arrays. The spiking activity of neurons was simultaneously coupled with the animal's position in the environment. Recordings were performed in different environmental conditions including presentation of objects. Our data suggest, unexpectedly, the presence of cells in anterior claustrum that are responsive to the position in space of the animal, to boundaries enclosing the environment and finally to the presence of objects in the environment. This novel claustral signal potentially directly modulates a wide variety of anterior cortical regions. We hypothesise that a key function of the claustrum is to provide dynamic information about body position, boundaries and landmark information, enabling dynamic control of behaviour.

Poster Ref: P3-D-047

Theme: D: Learning, Memory and Cognition

Encoding-related brain activity in transient epileptic amnesia.

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Patients with transient epileptic amnesia (TEA, a sub-type of medial temporal lobe epilepsy) often complain of accelerated long-term forgetting (ALF), despite performing within the normal range on standard neuropsychological tests and having clinically normal structural brain imaging. These patients typically exhibit normal learning and initial retention, but forget rapidly over subsequent days and weeks. Anterograde memory problems in TEA are presumed to reflect a deficit in hippocampus-dependent memory consolidation. However, this study was designed to investigate the possibility these patients suffer from a subtle encoding abnormality. In this fMRI study, we presented multiple photographs to a group of patients with TEA, who reported symptoms suggestive of ALF, and a group of controls. The patients actually demonstrated abnormally poor performance on a recognition test (outside the scanner) within 45 minutes of encoding. They produced more false alarms than the controls on both this test and another test four days later. In the left hippocampus, the patients showed a greater activity difference between subsequently remembered and forgotten items than that seen in the controls. Subsequently forgotten items were associated with less activity in this region in the patients than the controls. These results demonstrate brain activity abnormalities at the stage of encoding in TEA patients.

Poster Ref: P3-D-048

Theme: D: Learning, Memory and Cognition

Investigations in context-induced renewal: Effects of overtraining and NMDA receptor antagonism at memory retrieval.

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Introduction: Extinction results in the formation of new inhibitory memories rather than erasure of the original trace. For example, in context-induced renewal, returning animals to their training context after a period of extinction in a different context increases responding. Early in instrumental training animals' responding is sensitive to the value of its outcome and governed by action-outcome (A-O) associations. However, after extended training it becomes under control of stimulus-response (S-R) associations and insensitive to devaluation. Here it was investigated whether renewed responding undergoes a similar progression. The effects of blocking NMDA receptors at the time of retrieval of an A-O memory on renewal and expression of goal-directed responding were then investigated.

Methods: After 5 (Experiment 1) or 23 (Experiment 2) days training to respond for a sucrose or maltodextrin solution rats underwent extinction sessions in a novel context. Responding in training or extinction contexts was then tested following devaluation of the reinforcer used in training and an alternative reinforcer. Experiment 3: After 5 days training animals were injected with MK-801 (0.1mg/kg) or vehicle before undergoing an instrumental retrieval session. Animals were then extinguished and tested as above, before being given additional tests for both renewal and devaluation.

Results: Exp. 1 & 2: All animals showed a renewal effect ($p<.003$). Whilst animals that underwent 5d training showed a devaluation effect ($p=.003$), those given 23d training did not ($p=.76$). Exp. 3: Although the 5 minute retrieval session appeared to lead to extinction of the operant response, animals given MK-801 or vehicle at reactivation showed intact renewal ($p<.02$). Only animals given vehicle at reactivation reduced their responding in response to devaluation (vehicle: $p=.02$; MK-801: $p=.67$).

Discussion: Context-induced renewal undergoes a progression from being a goal-directed action to being an S-R habit. Blockade of NMDA receptors at the time of retrieval of an A-O memory prevented the expression of the devaluation effect at test, but did not affect overall responding. This suggests an A-O memory specific memory deficit, although further control experiments are necessary.

Poster Ref: P3-D-049

Theme: D: Learning, Memory and Cognition

Detecting significantly associated interactions with schizophrenia in a functional COMT1 pathway and their role in cognitive data.

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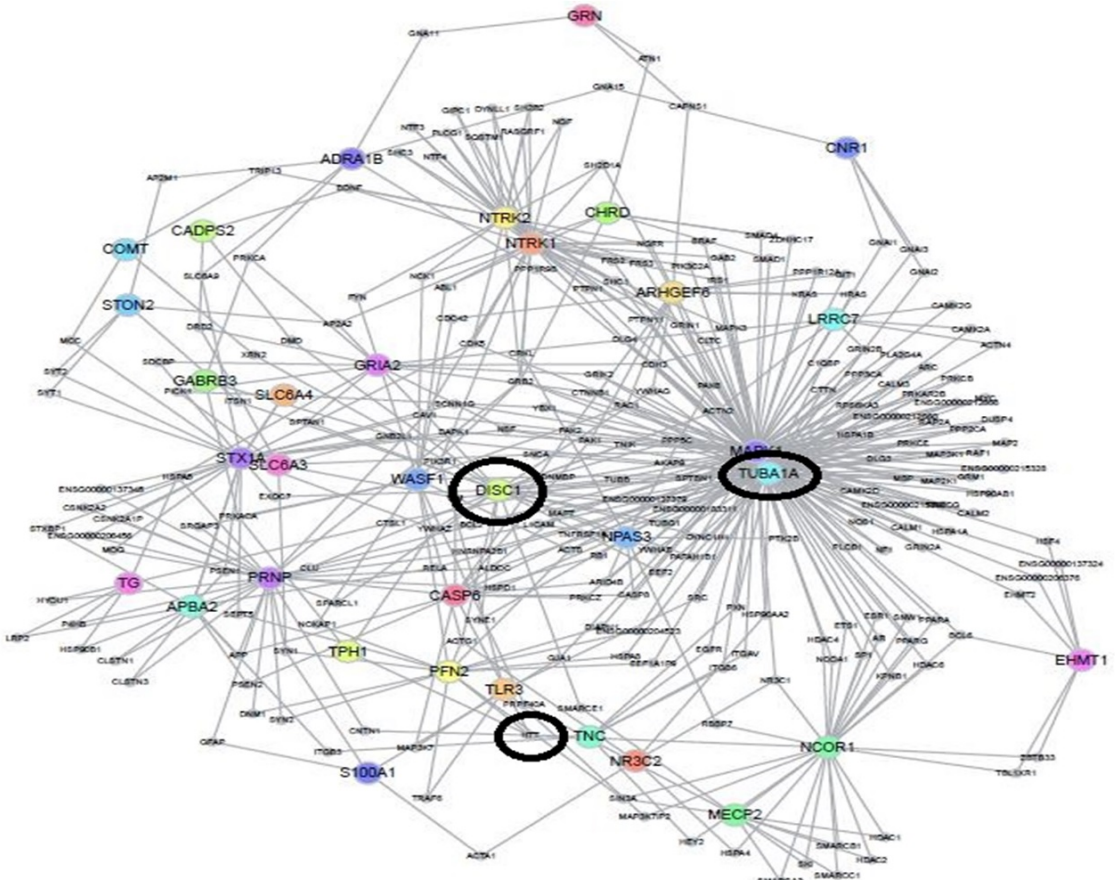
Schizophrenia (SCZ) is a complex disease characterized by impaired neuronal functioning. Catechol-O-methyl transferase (COMT) was related with psychiatric manifestations including SCZ and other psychoses. We performed our study in a functional COMT1 pathway (41 genes, 259 SNPs) to detect significantly SNP interactions associated with cognition, including 311 narrow psychosis and 74 broad psychosis.

RF algorithm has shown excellent performance in high dimensional data analysis. To test epistasis between functional SNPs (synonymous, missense and 3' and 5' UTR) , firstly, we performed RF to rank the top 30 SNPs of the training data. Secondly, we performed likelihood ratio tests (LRTs) between nested models in our independent test sample to test epistasis between the top 30 SNPs associated with SCZ in case status as well as between them in our cognitive study. To estimate the amount of variation explained, we used Nagelkerke's R2 in case-control status, and the R2 in cognitive. We detected SNP interactions associated with SCZ and cognitive variables. The most relevant significant 3-way SNP interaction, including the SNP - SNP interactions, was found in DISC1/TUBA1A/FOXP2 between the functional SNPs rs3082 (3'UTR), rs1056875 (missense) and rs12113612 (3'UTR), the top 5, top 27 and top 28, respectively, from the 500 runs of RF. This interaction was significantly associated with SCZ, and it was also detected to be associated with verbal IQ, and with IQ. In addition, taking into account only the 3-way interaction effect, significant interaction was detected between the same SNPs which influenced risk of SCZ (LRT p-value = 0.0132 and R2 = 1.05%). The interaction was again significantly associated with verbal IQ (LRT p-value = 0.0162 and R2 = 1.42%) and with IQ (LRT p-value = 0.0196 and R2 = 1.35%).

We found replication in the NIMH/Lieber Sibling Study that was associated with cognitive in a functional COMT pathway. DISC1 was detected to play a role both in SCZ and cognition. TUBA1A has a high expression in human fetal brain; neuronal migration disorders, which cause neurological and cognitive impairment, were associated with TUBA1A abnormalities. FOXP2 is a transcription factor that has been associated the development of speech and language.



Black circles = genes with significant interactions. Not shown: FOXP2 interacts with HTT

Poster Ref: P3-D-050
Theme: D: Learning, Memory and Cognition

Exploring changes of face recognition patterns across a full-night sleep.

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Introduction: Mechanisms of face recognitions have been studied for several decades. However, it has not been inspected how precisely initial face learning reflects subsequent face recognition patterns. Similarly, it has not been understood how precisely a full night sleep affects post-sleep face recognition patterns. We employed a new research paradigm to visualize face recognition patterns in quantifiable 2-dimensional spaces and examined what kind of features in the 2D spaces (*e.g.* distance or visual similarity between old and new stimuli) affects face recognition patterns. We also tested whether a delay of a full night sleep affects the visualized face recognition patterns compared to a non-sleep delay.

Methods: In this experiment, 32 subjects (16 female) were recruited. A half (8 female) of those was assigned as sleep group and the other half was assigned as wake group. We employed the AM-PM design, such that sleep group took a first session at 9PM then took a second session at 9AM, and vice versa; subjects were freed to go back home or to work/school during the 12 hours delay. Both groups took same face learning tasks and recognition tests.
Face stimuli: We established a set of face stimuli coordinated in quantifiable two dimensional spaces by allocating morphed facial features of age (from young to old) and gender (masculine to feminine) in x-axis and y-axis, respectively. Selected facial images were used in the learning tasks so that subjects learned facial images whose morphing patterns were limited within a specific area of the established 2D spaces. In the face recognition tests, all face stimuli were used to test which area in the 2D spaces was recognized as old stimuli.

Conclusion: By using this new research paradigm, we visualized face recognition patterns in 2D spaces. By inspecting various factors in the 2D spaces, we found that distance between old and new stimuli in the 2D spaces seemed to play a critical role in face recognition patterns. Sleep group also showed different recognition patterns from wake group. Although this study results are exploratory, follow-up investigations, for example which focus on a role of the distance in face recognition patterns, can verify if current results are replicable.

Poster Ref: P3-D-051

Theme: D: Learning, Memory and Cognition

Behavioural significance of altered connectivity within fronto-striatal loop circuits in Obsessive Compulsive Disorder.

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Introduction: The aim of this work is to test the hypothesis of dysfunction of discrete fronto-striatal-thalamic loop circuits in OCD patients and to relate patterns of altered connectivity to impaired performance on relevant cognitive tasks.

Methods: In study 1, we wanted to assess brain activation related to the attainment of a goal during planning and associated functional connectivity between cortical and striatal brain regions. To this end, 14 OCD patients, 13 of their unaffected first-degree relatives, and 13 matched controls were tested on an fMRI-optimized version of the Tower of London task. In study 2, multiecho resting state data were collected on an independent sample of 40 OCD patients and 37 matched controls, together with behavioural measures of planning and attentional set-shifting.

Results: In study 1, while performing planning task inside the scanner, OCD patients and their relatives achieved the same number of correct responses compared with controls at the expense of longer response times. Both patients with OCD and their relatives showed hypoactivation during planning, peaking in the right precentral gyrus and extending to the dorsolateral prefrontal cortex (DLPFC). No activation differences were found between OCD patients and their relatives. Psychophysiological Interaction analysis yielded reduced planning-related functional connectivity between the DLPFC and the putamen in OCD patients, and to a lesser degree in OCD patients' relatives, versus healthy controls. A qualitatively similar pattern of reduced functional connectivity between the DLPFC and caudate failed to reach significance.

Discussion: These results suggest that reduced planning-related activity in the right DLPFC is a candidate neurocognitive endophenotype for OCD. Hypoactivation of the right DLPFC and impaired functional connectivity with related subcortical brain structures might constitute an underlying neural substrate responsible for less efficient cognitive strategies in OCD and relate more generally to known deficits in goal directed behaviour. In study 2, we aim to further understand the behavioural significance of impaired functional connectivity within fronto-striatal-thalamic loops by addressing functional connectivity at rest and relating it to cognitive performance.

Poster Ref: P3-D-052

Theme: D: Learning, Memory and Cognition

The effect of stress and anxiety induced by CO_2 inhalation on the reaction to uncertainty and on efficiency in a free-operant two-lever choice task.

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Learning and reacting to uncertainty are closely linked to stress and anxiety. Here, we used CO2 to induce stress and anxiety and measured performance in a free-operant task involving uncertainty with reward and punishment conditions. A parallel version of this task was recently validated in rodents.

Healthy volunteers (n=43) performed a free-operant two-lever choice task while breathing through a mask in a randomized placebo-controlled within-subject design. They completed 2 sessions while inhaling normal air (placebo) and air enriched with CO_2 (7.5%, 21% O_2, N_2, counterbalanced order). They could press either lever to earn rewards (sound, £0.50), but only one lever was active, changing randomly over time. A third lever (observing) informed about the currently active lever (cost £0.05). In each session a standard block was followed by a block where pressing the inactive lever was punished intermittently (sound, -£0.50). To validate the CO_2 response, we measured physiological (heart rate, blood pressure) and subjective reactions (visual analogue scales (VAS) e.g. anxiety). Mixed ANOVAs tested for the effects of punishment and CO_2 (within-subject factor) and CO_2 administration order (between-subjects factor) on observing, total money earned, efficiency and active lever reaction time immediately following the observing cue, and the physiological and VAS measurements.

Physiological and VAS measurements were higher during CO_2 inhalation. Choice efficiency and observing were increased by possible punishment, but we found no additional effect of CO_2 and no learning effect on efficiency over the session. All participants showed a learning effect, *i.e.* earned more money during the second session. When first exposed to air, participants gradually responded quicker to the observing cue with the subsequent punishment and then the CO_2 session. When first exposed to CO_2, participants were faster initially, maintaining this fast responsiveness throughout the experiment.

The data indicate that stress and anxiety led to quicker reactivity towards the observing cue, but did not alter overall efficiency and learning in the free-operant task. This could be mediated by increased attention towards a cue allowing participants to reduce uncertainty.

Poster Ref: P3-D-053

Theme: D: Learning, Memory and Cognition

Spatial navigation, familiarity, anxiety and effects of dizocilpine.

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In a 3D maze, which is a modified version of the radial arm maze, avoidance of the distal segment of the arms is used as an indicator of anxiety. Balb/c mice require four to five sessions to venture onto the distal segments of the maze while C57/BL6J and CD-1 mice require one to two sessions, respectively.

The 3D maze (Grey PVC, 5 mm thick) consists of nine arms radiating from a central platform. Each arm (51 cm x 11.2 cm) is made from two segments, extended from a nonagonal shaped central hub. The first segment of an arm (15.2 cm x 11.2 cm) directly attached to the central platform can be tilted and constitutes a bridge that allows access to the second segment (35 cm x 11.2 cm) of the arm. In the present experiment, the bridge to each arm forms a slope which is inclined upward by about 40º. All parts of the maze apparatus are unprotected; hence mice are exposed to a complete open space.

In the present study, we examined the effect of MK-801 (0.1 mg/kg i.p) in C57BL/6J mice trained in a 9 arms radial maze. The experiment involved 3 groups of food-deprived mice which were introduced to the maze without preliminary habituation. They were trained to retrieve a food pellet located at the end of each of the 9 arms of the maze in six consecutive sessions, one session a day. One group received saline while a second group received MK-801 for 6 sessions. A third group received saline in the first 3 sessions and MK 801 in each subsequent session. Saline and MK-801 were administered 30 min before each test session.

All saline treated mice made numerous visits to the arms while MK treated for 6 days showed reduced entry onto the arms. MK-801 had no effect on arm entries in mice treated on the fourth day onward. Examination of the first 9 arm choices revealed that the number of repeated arm entries (memory errors) was significantly increased in MK-801 treated for 6 days but not in mice which received saline before MK-801 treatment.

The present results appear to confirm that MK801 produces spatial navigation deficit in animals that are unfamiliar with the test environment.

Poster Ref: P3-D-054

Theme: D: Learning, Memory and Cognition

A novel touchscreen serial reversal task to study the neuropharmacology of visual reversal learning in rats: Effects of lateral orbitofrontal cortex manipulations and of systemic treatment with the dopamine D2/D3 agonist, quinpirole.

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University of Cambridge

Impaired cognitive flexibility in touchscreen-based tasks of reversal learning (*e.g.* within the intradimensional/extradimensional task in the CANTAB battery) has been linked to schizophrenia, obsessive-compulsive disorder, drug addiction, and (medicated) Parkinson's disease. Current treatment for these conditions are mostly ineffectual in improving such cognitive impairment. To investigate the neural basis of cognitive inflexibility and to identify targets for potential pharmacological treatment, valid animal tests of reversal learning are required. To this end, we developed a touchscreen-based serial visual reversal learning task for rats. Rodents were trained to discriminate between two stimuli (*e.g.*, CS+ vertical bars, CS- horizontal bars) on a touchscreen to receive sucrose reward. Contingencies alternated (*e.g.* CS+ horizontal bars, CS- vertical bars) until rats consistently completed each reversal within three days. At this stage of stable performance, the protocol allowed systemic or intracranial pharmacology in a within-subject design. We confirmed the utility and the construct validity of the task by observing impaired early reversal performance after infusions of a baclofen/muscimol cocktail into the lateral orbitofrontal cortex in one cohort of rats, and improved early performance after infusing the serotonin 2C-receptor antagonist, SB242084, into this brain structure of another cohort. In addition, systemic injections of the dopamine D2/D3 receptor agonist, quinpirole, impaired performance on the task in a third cohort. The combination of high face- and construct validity suggests that this touchscreen-based experimental paradigm may be useful in exploring the neural circuitry and neuropharmacology of reversal learning, of relevance for psychiatric disorders and Parkinson's disease.

Poster Ref: P3-D-055

Theme: D: Learning, Memory and Cognition

In vivo electrophysiological signatures of the nmdar antagonists ketamine & lanicemine are compared with those of serotonergic compounds (DOI, LSD) to give insights into the mechanisms underlying antidepressant activity and psychosis.

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Eli Lilly, Windlesham

NMDAR antagonists such as ketamine have complex, yet intriguing properties when administered systemically to humans. Acutely, they can induce psychomimetic symptoms, while their antidepressant actions arise within hours of first treatment. The mechanisms underlying both of these effects are largely unknown. We therefore applied *in vivo* electrophysiological techniques to awake rats with the aim of identifying commonalities in the responses associated with each class of compound and ultimately elucidating how different neuronal networks contribute to the effects.

Rats were implanted with either 32 channel linear silicon probes targeting the mPFC and hippocampus (n=10) or skull screws over the frontal and occipital cortices (n=32). Depth recordings were performed in an open field arena, whereas EEG recordings were performed in the animals' home cages with the SCORE system utilised to quantify EEG power, LMA and sleep state continually across multiple days pre/post treatment.

The NMDAR antagonist ketamine (10 & 30mg/Kg i.p.) modulated LFP power across multiple frequency bands, with prominent spectral peaks occurring post-drug in the gamma (40-80Hz) and HFO (140-180Hz) ranges. Notably, there was an analogous increase in gamma power following administration of the low-trapping NMDAR antagonist lanicemine (10, 30 & 60mg/Kg i.p.), but no corresponding increase in HFO oscillations. Furthermore, lanicemine had no effect on LMA, whereas ketamine treatment elevated it. These disparities potentially relate to lanicemine's lower propensity for eliciting psychomimetic symptoms in humans relative to ketamine. In contrast to ketamine, the 5HT2 agonists DOI (1 & 3mg/Kg s.c.) and LSD (0.1 & 0.3mg/Kg i.p.) had more specific effects on LFP/EEG power, where they induced HFO, but not gamma frequency oscillations.

This data highlights the diverse effects that psychomimetic compounds have on oscillatory activity in the rat brain. Correlating these changes with the specific profile of psychomimetic effects elicited by the same compounds in humans may identify potential biomarkers that can facilitate the development of both antidepressant compounds that avoid any unwanted psychomimetic side-effects in addition to novel anti-psychosis medication.

Poster Ref: P3-D-056

Theme: D: Learning, Memory and Cognition

Fearful faces have a sensory advantage in the competition for awareness.

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Threat signals, such as fearful faces, are particularly salient to the human visual system (Adolphs, 2008, Curr Opin Neurobiol, 18, 166-172). Recent findings suggest that fearful faces can be evaluated without awareness and are preferentially promoted to conscious perception (Yang *et al.*, 2007, Emotion, 7, 882-886). This is in agreement with evolutionary theories that posit a dedicated, sub-cortical pathway specialised in the processing of threat-relevant signals (Tamietto *et al.*, 2010, Nat Neurosci, 11, 697-709). Here, we propose an alternative explanation for the widely reported “fear advantage”. Using the public contrast sensitivity dataset "ModelFest" (Watson *et al.*, 2005, J Vision, 5, 6, 717-740) we show that fearful faces have higher contrast energy at the spatial frequencies humans are sensitive to, relative to neutral faces. This "effective contrast" advantage is stable across viewing distances that characterise typical social interactions. Subsequently, in two visual detection paradigms, Continuous Flash Suppression (CFS) and visual masking, we show that effective contrast, but not perceived valence or arousal predicts conscious perception of facial expression signals. Importantly, our findings do not support the existence of a specialised threat-detection mechanism that promotes potentially threatening stimuli to awareness. Rather, our data suggest that selective pressures have moulded the fearful facial expression to exploit the sensitivity of general-purpose sensory mechanisms.

Poster Ref: P3-D-057

Theme: D: Learning, Memory and Cognition

The cyclin-dependent kinase 5 activator, p25, enhances hippocampus-dependent memory and synaptic plasticity.

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Cyclin-dependent kinase 5 (Cdk5) is a proline-directed protein kinase that has been implicated in a range of neurobiological processes including neuronal development, synaptic plasticity and the mechanisms of drug addiction. More recent evidence indicates that dysfunction of Cdk5 is involved in the pathology of neurological and neurodegenerative disorders, including Alzheimer's disease (1). Cdk5 is activated by binding to one of its two regulatory subunits, p35 or p39, which largely restrict Cdk5 activity to neurons. Alterations in calcium homeostasis during neuronal stress and neurotoxicity can induce calpain-mediated p35 cleavage and p25 formation. p25 also binds to Cdk5, but unlike p35 is not readily degraded. Formation of a Cdk5/p25 holoenzyme alters Cdk5 cellular location, substrate specificity and kinase kinetics. Prolonged expression or high levels of p25 have been found to impair learning and memory (L&M) and the induction of long-term potentiation (LTP) (2). However, a transient increase or low levels of p25 expression have been shown to enhance L&M and LTP (2, 3). Interestingly, brain specific Cdk5 knockouts also have improved L&M and enhanced LTP (4). To investigate the role of synaptic activity-dependent physiological p25 generation in plasticity and cognition, we assessed the effect of transgenic low-level p25 expression on behavioural, neurophysiological and biochemical parameters relevant to L&M function. We found that p25 transgenic mice had improved hippocampus-dependent L&M in the Morris Water Maze and novel object recognition tasks, and a reduced threshold for LTP induction. Furthermore, phosphorylation of the NMDA receptor and changes in the activity of the cAMP/PKA signaling cascade were altered in the hippocampus of these mice. Together these results suggest that p25 mediates synaptic plasticity and memory formation *via* the control of NMDA receptors. These studies support the idea that neural disorders may stem from the dysregulation of synaptic remodeling mechanisms and that alterations in Cdk5/p25 activity may contribute to pathophysiology.

1.Cheung and Ip (2012) Trends Cell Biol 22:169-175; 2.Fischer *et al.* (2005) Neuron 48:825-838; 3.Angelo *et al.* (2003) Eur J Neurosci 18:423-431; 4.Haswali *et al.* (2007) Nat Neuro 24:2433-2435

Poster Ref: P3-D-058

Theme: D: Learning, Memory and Cognition

Structural brain connectivity and cognitive ageing in the lothian birth cohort 1936.

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Cognitive decline in normal ageing may in part be due to cortico-cortical disconnection caused by white matter deterioration. Here we present results from a pilot study examining links between brain structural connectivity and cognitive ability in a group of subjects with cognitive measures from both childhood (11 years) and older (73 years) age. Diffusion and structural MRI were obtained from 88 community-dwelling male participants of the Lothian Birth Cohort 1936 at age 73 years (mean +/- SD: 73.09 +/- 0.39 years). Structural fractional anisotropy (FA) weighted networks were determined for each subject using grey matter parcellations obtained from Freesurfer. White matter tracts were created using FSL's Bedpostx/Probtrackx with a two-fibre model. Three global metrics of brain connectivity were obtained from the connectivity matrices: clustering coefficient, mean shortest path length and global efficiency. Linear regression analyses were used to study associations between these connectivity metrics and three important domains of cognition: memory (WMS III Logical Memory, Verbal Paired Associates, Spatial Span), information processing speed (Simple and Four choice reaction time, Inspection Time, WAIS III Symbol Search, Digit Symbol-coding) and fluid intelligence (WAIS III Matrix Reasoning, Block Design, Letter-Number Sequencing, Digit Span Backwards). General factors for each cognitive domain were extracted using PCA; age in days and childhood IQ were corrected for in all models. Results are presented as effect size (standardised beta); p-value.

Only processing speed was significantly associated with the three connectivity metrics: clustering coefficient (beta=0.26; p=0.012), mean shortest path length (beta=0.23; p=0.027) and global efficiency (beta=0.26; p=0.010). The connectivity metrics were all highly correlated with each other (beta=0.89-0.97), and with a general factor of white matter FA obtained from tractography of 14 major tracts (beta=0.65-0.82).

These results show that processing speed is the cognitive domain most affected by global white matter structure in older age. Further research will investigate the relationship between information processing speed and brain connectivity taking into account factors such as spatial distribution and occurrence of white matter lesions.

Poster Ref: P3-D-059

Theme: D: Learning, Memory and Cognition

Transcranial alternating current stimulation can improve declarative memory.

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Declarative memory has been associated with the reinstatement during remembering of the same patterns of cortical activity observed at encoding. A recent study demonstrated that neural oscillations are also reinstated in a frequency specific manner for successfully retrieved memories. Our experiment aimed to investigate these findings by looking at the effect of interactions between oscillatory activity at encoding and retrieval on declarative memory. Transcranial alternating current stimulation (tACS) was applied over the left dorsolateral prefrontal cortex (DLPFC) to induce oscillatory activity during encoding and retrieval phases of an old-new recognition memory task. Sixty-seven participants took part in two testing days, one in which they were stimulated throughout the encoding and retrieval phases (Active condition) and one in which they were stimulated for only a few seconds (Sham condition). Four separate groups were tested at different frequencies in the gamma range (60 and 90Hz). They were stimulated with either the same frequency during encoding and retrieval phases (Congruent stimulation condition) or different frequencies (Incongruent stimulation condition); *i.e.* 60 and 90 Hz in the encoding and retrieval phases respectively, and vice versa for the incongruent conditions. We found that while incongruent tACS did not modulate memory performance, congruent tACS increases memory performance significantly more than sham stimulation. These results suggest that the reinstatement of oscillatory activity over the left DLPFC can significant benefit declarative memory performance. It also suggests that gamma-frequency oscillations in the DLPFC are essential in declarative memory processing.

Poster Ref: P3-D-060

Theme: D: Learning, Memory and Cognition

One hemisphere, two languages.

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Over the past 20 years, converging evidences from studies on patients with brain lesions and investigations of linguistic processing in healthy individual suggest an important role of the right hemisphere in language processing.

Main purpose of this study is to describe the cognitive and linguistic profile of AC, a 24 years old bilingual person (Speaking Romanian and Italian) who, after a severe traumatic brain injury, reported a large left ventricular dilation, involving fronto temporo parietal regions. As a consequence, AC is now recovering both languages relying only on his right hemisphere. In view of these aspects, this case provides a unique opportunity to assess the role of the right hemisphere in language recovery after acquired brain injury. The first part of the study consisted of a battery of tests aimed at assessing AC's cognitive and linguistic skills.This battery was administered first in October 2010 and then in August 2012. Furthermore, in 2013 AC's bilingual profile was explored in both the languages by administering the questionnaire contained in the first section (Part A) of the Bilingual Aphasia Test and the Italian and Romanian version of the Western Aphasia Battery.Results of the neuropsychological assessment showed a general cognitive improvement, more evident in the latest assessment. With regard to AC's bilingual evaluation, it highlighted the presence of a mild fluent aphasia, characterized by the presence of comparable difficulties in linguistic production in both languages. Comparable impairments across the two languages were found also in Reading and Writing. As for Comprehension, the two languages were both mildly affected but with sligh different levels of gravity.

In conclusion, in spite of the severity of the lesion, AC has shown a parallel recovery of his two languages and of some cognitive skills. This case report sheds new light on the dynamic regulation of interhemispheric interactions. These findings are of particular importance for understanding language recovery after stroke to the left hemisphere, as they suggest that the right hemisphere has the intrinsic potential to take an active role in language recovery after stroke, through an increased functional influence of the dysfunctional left hemisphere language network.

Theme E: Sleep, Circadian and Neuroendocrine Mechanisms

Posters P3-E-001 to P3-E-017

Poster Ref: P3-E-001

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

An epigenetic switch controls retinoic acid activation of hypothalamic growth-/feeding-related genes.

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The vitamin A-derived hormone retinoic acid (RA) regulates gene expression *via* binding to members of the nuclear receptor family. Retinoic acid is best known for its essential role in development, but RA signalling is also active in some regions of the adult brain. One such region is the hypothalamus, which maintains balance in various processes and behaviours such as metabolism, feeding and body weight. Retinoic acid is synthesised by retinaldehyde dehydrogenase 1 (RALDH1) in the tanycytes that line the third ventricle adjacent to the hypothalamus, but its function there is not well understood. In animals that show seasonal changes in body weight and feeding, such as hamsters and the F344 rat, hypothalamic levels of retinoic acid are highest and RA signalling most active at times of increased growth and food intake. This suggests a role for RA in the regulation of energy balance. To explore the actions of retinoic acid in the hypothalamus, an *ex vivo* hypothalamic rat slice culture method was developed. This maintains the integrity of the hypothalamic nuclei as well as the RALDH1-expressing tanycytes and provides a powerful method to examine the direct effect of hormones and regulatory factors on the hypothalamus. In the cultured hypothalamus, RA increased hypothalamic expression of several genes associated with increased food intake and growth, including GHRH and AGRP. Epigenetic regulation of gene expression is thought to control several hypothalamic functions and RA signalling is a pathway known to be regulated by histone deacetylase (HDAC) inhibitors. Treatment of slices with the class I/II HDAC inhibitor trichostatin A (TSA) potentiated the effect of RA on GHRH expression, but not AGRP expression. Sirtinol, a class III HDAC inhibitor, had no effect on RA-regulated gene expression. These data demonstrate that hypothalamic RA acts to regulate the expression of genes associated with increased growth and feeding. In addition, epigenetic modulation of RA signalling by class I/II HDACs in the hypothalamus may further contribute to the control of body weight and feeding.

Poster Ref: P3-E-002

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

Would the real effects of intranasally administered oxytocin please stand up?

Frances Vaughan[1], Gareth Leng[2] and Mike Ludwig[2]

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Intranasal administration of the neuropeptide oxytocin (OT) has been widely used to study the role of this peptide in human behaviour. However, it remains unclear whether intranasally administered OT accesses the brain from the nasal cavity, or whether it enters the peripheral circulation and acts primarily at receptors in other organs. Clarifying the mechanism by which intranasal OT mediates the observed behavioural effects has implications for realising the therapeutic potential of this treatment, and for understanding the endogenous neuropeptide system. To address this question, we conducted a meta-analysis of 94 human studies examining the physiological (13 studies) and behavioural (81 studies) effects of intranasal OT administration. Included studies were randomized controlled trials of intranasal OT vs placebo, published between 01/2005 and 06/2014. Participants were male (n = 2247) and female (n = 851; unspecified = 444), healthy (n = 3046) and non-healthy (n = 496). Analyses were performed under the random-effects model with all effects of OT considered positive, as primary outcome measurements differed between trials. Results showed that intranasal OT has a moderate effect on both behavioural and physiological measurements, although point estimate Hedges' g effect size was larger in behavioural studies (g = 0.725; 95% CI: 0.370, 0.668) than in physiological studies (g = 0.519; 95% CI: 0.626, 0.823) (p = 0.024). No significant difference in effect size was found between male and female participants, nor between healthy and non-healthy participants. However, we found a positive correlation between dosage and effect size in behavioural studies ($p<0.01$), and a negative correlation between effect size and sample size in both behavioural and physiological studies ($p<0.05$). These results indicate that intranasally administered OT has significant effects on human physiology as well as behaviour, although the magnitude of reported effects may be inflated in small samples. We propose that intranasal OT elicits its physiological effects through direct action at receptors in the periphery, and that some behavioural effects of intranasal OT may be secondary to these peripheral effects.

Poster Ref: P3-E-003

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

A new function for the pineal gland and control of nightly melatonin rhythm.

Anna Ashton, Patrick Stoney and Peter McCaffery

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The pineal gland is situated at the midline of the brain and produces melatonin, the hormone responsible for signalling darkness to the body and entraining daily physiological rhythms. Melatonin is a broadly acting hormone with receptors in peripheral organs and various central nervous system regions. Changes in melatonin production and signalling are associated with a number of diseases including type 2 diabetes and breast cancer, it is therefore important to understand how melatonin synthesis is regulated. The nightly production of melatonin is induced by upregulation of arylalkylamine N-acetyltransferase (AANAT) gene expression and activity, the rate-limiting enzyme for melatonin synthesis. Studies have shown there are high levels of retinol (vitamin A) in the mammalian pineal gland and that vitamin A deficiency causes a reduction in AANAT and melatonin levels. The effects of retinol are mediated by the active metabolite retinoic acid, a potent regulator of gene transcription. This study aims to confirm whether retinoic acid signalling components are present and function in the pineal gland and determine whether retinoic acid controls melatonin production. Organotypic culture of *ex vivo* rat pineal glands is being used to study this alongside qPCR and immunohistochemistry. We have found that retinoic acid receptors and key synthetic enzymes are present in the rodent and human pineal gland, some of which exhibit diurnal (day/night) changes in expression suggesting rhythmic production of retinoic acid in this gland. We have also shown that retinoic acid can upregulate Aanat expression, suggesting that retinoic acid has a role in the regulation of melatonin synthesis.

Poster Ref: P3-E-004

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

5-HT2CR agonist obesity medication increases the activity of appetitive brain stem neurons.

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Rowett Institute of Nutrition and Health, University of Aberdeen

The brain plays an essential role in the regulation of food intake and energy balance. This vital regulatory process is coordinated *via* the interaction of numerous brain regions. Amongst these is the nucleus of the solitary tract (NTS), a brain stem region that integrates satiety signals from the gastrointestinal tract and related digestive organs. 5-hydroxytryptamine (5-HT; serotonin) is a neurotransmitter involved in the regulation of energy homeostasis mainly *via* its action at the 5-HT2C receptor (5-HT2CR). This receptor is amenable to pharmacological manipulation for obesity treatment, as illustrated by the new obesity medication lorcaserin, which is a 5-HT2CR agonist. We utilised immunohistochemistry (IHC) in a reporter 5-HT2CR-yellow fluorescent protein (YFP) mouse line to map 5-HT2CR distribution and characterise its expression within the NTS. We report that 5-HT2CRs are most abundantly expressed in the medial-caudal NTS, a sub-region expressing energy balance regulating pro-opiomelanocortin (POMC) neurons. We observed that 5-HT2CRs are anatomically positioned to influence the activity of POMC cells. Furthermore, we observed that 5-HT2CR agonist obesity treatment lorcaserin increases c-fos immunoreactivity (a marker for neuronal activation) in NTS POMC neurons. These findings reveal that 5-HT2CR agonist obesity treatment lorcaserin influences the activity of appetitive NTS POMC neurons and this may be a mechanism through which its therapeutic effect is achieved.

Work was supported by the Wellcome Trust (WT09801) and BBSRC (BB/K001418/1).

Poster Ref: P3-E-005

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

Trans-generational effects of maternal exposure to social stress on anxiety-like behaviour in rats.

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Background: Prenatal Stress (PNS) exposure has been shown to affect many traits in the first filial generation including increased anxiety-like behaviour. Little is known about transfer of this trait to the next generation.

Aim: To investigate whether the anxiogenic effects of PNS exposure and alterations in gene expression in the brain associated with an anxious phenotype are transmitted to the second filial generation.

Methods: Pregnant rats were exposed to social stress (resident-intruder paradigm) for 5 days during the last week of pregnancy. The female PNS offspring were mated at 3 months of age with control stud males and left undisturbed throughout their pregnancy. The second generation (F2) offspring were studied from birth until 6 months of age. Anxiety-like behaviour was investigated using: the open-field test (OFT), light-dark box (LDB) and elevated plus maze (EPM). Differences in mRNA expression for corticotropin releasing hormone (Crh) and its receptors (Crhr1 and Crhr2)in the amygdala were analysed using *in situ* hybridization. Body weight was monitored throughout.

Results: F2 rats had lower birth weight compared to controls and this was maintained throughout the lifetime. The F2 males exhibited significantly greater anxiety-like behaviour in the LDB and EPM compared with control males. There was no difference in anxiety-like behaviour between control and F2 females during metestrus/diestrus. At proestrus/estrus, control females displayed a reduction in anxiety-like behaviour, but this effect of estrus cycle stage was not observed in the F2 females. Crh mRNA expression was significantly greater in the central nucleus of the amygdala in F2 males compared with controls, but not in F2 females. Moreover, Crhr1 mRNA expression was significantly increased, whereas Crhr2 was significantly decreased in discrete regions of the amygdala in F2 males compared with controls, but not in the F2 females.

Conclusions: Some of the effects of prenatal stress can be transferred to the next generation. Previously we showed that PNS increases anxiety-like behaviour in F1 male rats and we now show that without further intervention this effect can be transmitted to the F2 generation, in a sex-dependent manner.

Financial support: BBSRC and BSN.

Poster Ref: P3-E-006

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

Synaptic plasticity during cortical slow-wave activity.

Julian Bartram, Martin Kahn, Simon Tuohy, Antonia Langfelder and Edward Mann
University of Oxford

Sleep is a ubiquitously occurring behavioural state, and yet, we are only beginning to understand its underlying processes. Our goal was thus to shine light on the cellular and synaptic function of cortical slow waves, which are the predominant pattern of activity during deep sleep. Employing advanced electrophysiological recording techniques and two-photon Ca^{2+} imaging in an *in vitro* model of slow waves, we identified a synaptic depression mechanism that could play a crucial role in the phenomena of synaptic homeostasis and synaptic pruning.

Poster Ref: P3-E-007

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

Remodelling of the seasonal neuroendocrine axis by a circannual clock, driven by a binary cellular switch mechanism in the pituitary gland.

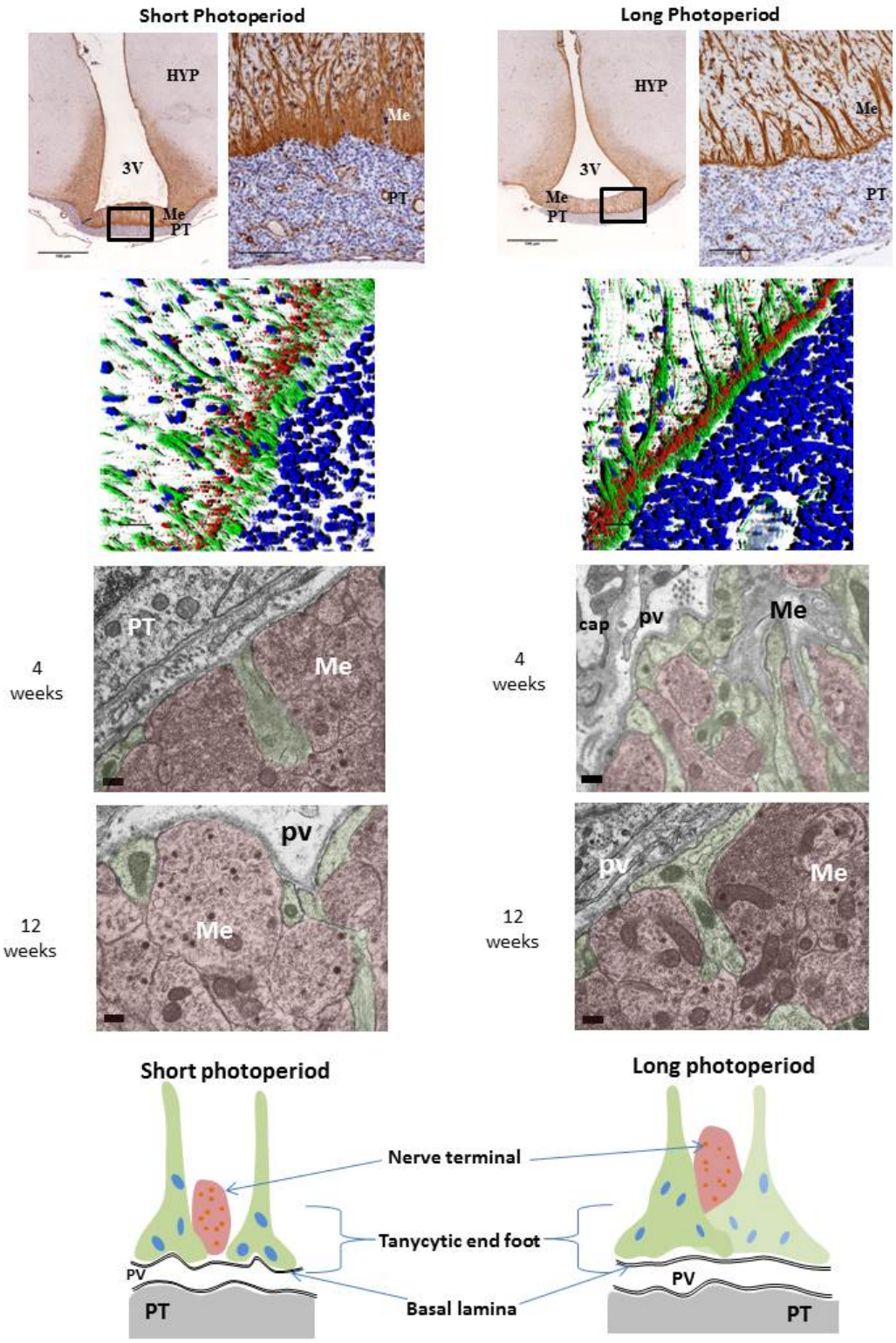
Shona Wood[1], Helen Christian[2], Katarzyna Miedzinska[3], Mark Johnson[2], Le Yu[3], Bob Paton[3], Ben Saer[1], Judith McNeilly[4], Julian Davis[5], Alan McNeilly[4], David Burt[3] and Andrew Loudon[1]

[1]Faculty of Life Sciences, University of Manchester, [2] Department of Physiology, Anatomy and Genetics, Oxford University, [3]The Roslin Institute, University of Edinburgh, [4]MRC Centre for Reproductive Health, Queen's Medical Research Institute, Edinburgh, [5]Faculty of Medical and Human Science, University of Manchester

In seasonal mammals, lengthening photoperiod (LP) stimulates thyroid hormone (TH) conversion in ependymal tanycytes lining the 3rd ventricle of the hypothalamus, thus timing breeding seasons. TH is activated on LP by thyroid-stimulating hormone (TSH) from the adjacent pituitary pars tuberalis (PT), driven by the transcriptional co-activator EYA3, which operates as a TSH on-switch. While mechanisms involved in the photoperiod input pathway are partially resolved, the nature of the neuroendocrine cascade involved in generating long-term circannual cycles remains poorly understood. Using a seasonal breeder, the sheep, we characterized the state of individual thyrotroph cells in the PT and the tanycyte/neuronal interactions in the median eminence (ME) at different phases of the endogenous cycle.

We undertook extensive anatomical studies at the light and EM-level which revealed dramatic wide-spread re-modelling of cell morphology in the PT and adjacent ME, but no evidence of *de novo* cell division, in response to photoperiod. We also noted that our PT RNA-seq data was strongly enriched for molecules normally associated with axon guidance, neurogenesis and morphogenic signalling. This suggested a potential role for the PT in signalling to the adjacent neuroendocrine secretory cells of the ventral hypothalamus. In the reproductive inactive phase of the cycle, we find that the end-feet of the ME tanycytes engulf the nerve terminals, possibly preventing GnRH release and downstream reproductive changes. Finally, we characterized the changes of EYA3 and CHGA mRNA and protein expression in individual PT cells, at different phases of the circannual cycle, revealing LP-induced co-expression of EYA3/TSH and SP induced expression of CHGA in PT thyrotrophs.

Our results demonstrate that the PT and hypothalamus are remarkably plastic, with clock-driven re-modelling of the neuroendocrine axis driving circannual rhythms.



The relationship between nerve terminals and tanycytes in the ME. GnRH and Vimentin (tanycytes) immunostaining of the hypothalamus rendered into 3D image. Electron micrographs of ME nerve terminals and tanycytes. In SP the nerve terminals are in contact with the basal lamina and the tanycytes have retracted from the ME, the opposite is true in LP, where the tanycytes encase the nerve terminals.

Poster Ref: P3-E-008

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

Diurnal changes in ingestive behaviour: Monitoring food "Micro-Intake" events in mice provides essential information.

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Measurement of food intake by small experimental animals like mice or rats is typically performed gravimetrically. The mass of a food hopper is monitored, and the abrupt increase in the variance of the hopper mass that signals an intake event is detected. The decrease in hopper mass following the re-establishment of mass stability equals the mass of food removed.

However, the low mass resolution of most intake monitoring systems (usually 10-20 mg) dictates the smallest intake event that can be detected. Using a high resolution food intake monitoring system with a detection limit of 2 mg (Sable Systems Promethion) we show that many intake bouts occur below the detection threshold of conventional food intake monitoring and metabolic phenotyping systems.

The food uptake of 8 male C57BL/6 mice kept at a diurnal cycle 12h/12h was measured at 6 different temperatures ranging from 19 – 29 °C. “Micro-intake” events (here defined as a single event with a food intake between 2 and 20 mg) typically lasted for < 2.5 min, with some lasting < 1 min. Micro-intake events comprise 20-50% of total intake events. Within the light-cycle about 70% of all intake events occurred during the night-phase. However, the proportion of micro-intake events to total intake events was higher during the day-phase then during the night-phase. This uptake pattern was shown by each individual mouse and did not change with temperature or, thus, with metabolic flux rates.

Although the contribution of “micro-intake” events to total food intake amounts is relatively minor, each corresponds to a decision to initiate intake followed by rapid satiety and termination of feeding behaviour. Micro-intake events cannot be ignored if a complete understanding of model animal feeding behaviour is desired.

Poster Ref: P3-E-009

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

Mineralocorticoid and glucocorticoid receptor-mediated control of rat hippocampal glucocorticoid-inducible gene transcription after acute stress.

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Thirty years ago we discovered that glucocorticoid hormones bind to mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs) in the brain (Reul & De Kloet 1985 Endocrinology 117:2505-11). These receptors play a vital role in the regulation of physiological and behavioural responses under baseline conditions and after stress. Glucocorticoid-inducible genes in the brain (like Per1, Sgk1 and Fkbp5) are thought to be involved in these responses. Presently, however, little is known about the role of MRs and GRs in the expression of these genes at the genomic level *in vivo*.

Male Wistar rats were killed direct from their home cage as baseline controls or forced to swim in a glass beaker filled with water at 25°C for 15 min after which they were killed at either -15min, 30min, 60min or 3h after start of swimming. In separate experiments, rats were pre-treated with either RU486 (a GR antagonist) or vehicle 30 min prior to forced swimming and killed 30 min after the start of swimming. Tissue samples were either used in chromatin immuno-precipitation (ChIP) studies to assess binding of the receptors to Glucocorticoid-Response Elements (GREs) within target genes (Per1, Sgk1, Fkbp5) or for mRNA analyses by RT-PCR.

After forced swim stress we observed significant transient rises in MR and GR binding to GREs within the hippocampal Per1, Sgk1 and Fkbp5 genes. These findings were associated with time-dependent increases in mRNA expression of these genes. Surprisingly, preliminary data showed that RU486 had no significant effect on either MR or GR binding to these GREs and failed to prevent the stress-induced increases in Per1 and Sgk1 mRNA responses.

Thus, MRs and GRs bind directly to specific recognition sequences within glucocorticoid-inducible genes under both baseline conditions and following acute stress. It appears that under stress conditions RU486 is unable to prevent GR binding to the GREs, which may underlie the failure of RU486 to inhibit stress-induced transcription of these glucocorticoid-inducible genes *in vivo*. Furthermore, other stress-induced transcription factors may be acting on these genes that may compensate for any loss of GRE-mediated transactivation after RU486.

This study is funded by the BBSRC.

Poster Ref: P3-E-010

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

5-HT2CR activation of brainstem pro-opiomelanocortin neurons suppresses appetite.

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Obesity is a primary healthcare challenge of the 21st century. Medications increasing the bioavailability of the neurotransmitter 5-hydroxytriptamine (5-HT, serotonin) improve obesity. 5-HT primarily influences appetite *via* action at the 5-HT2C receptor (5-HT2CR; Htr2c); the clinical significance of which has recently been affirmed with the launch of the 5-HT2CR agonist lorcaserin for obesity treatment. Efforts to determine the mechanism of 5-HT2CR appetite suppression have largely focused upon melanocortin signalling from pro-opiomelanocortin (Pomc) neurons in the hypothalamus. However, a second population of Pomc neurons is found in the nucleus of the solitary tract (NTS). To investigate the specific contribution of NTS 5-HT2CRs to appetite we utilised a 5-HT2CR-Cre:yellow fluorescent protein (5-HT2CRCre) mouse line and a Pomc-dsRed reporter mouse line. Histochemical analysis determined that 5-HT2CRs are anatomically positioned to influence PomcNTS activity. Using patch-clamp electrophysiology, we then demonstrated that 5-HT and 5-HT2CR agonists directly depolarise and increase the firing rate of approximately 40% of PomcNTS neurons. To examine the physiological significance of these findings we utilised designer receptors exclusively activated by designer drugs (DREADD) to probe the effect of selectively activating NTS 5-HT2CR neurons on eating behaviour. Specifically, a virus that transduces designer Gq receptor (AAV8-hSyn-DIO-hM3Dq-mCherry) was bilaterally injected into the NTS of 5-HT2CRCre mice producing 5-HT2CRCre:hM3Dq-expressing neurons exclusively within the NTS. The selective activation of these neurons by the designer drug clozapine-N-oxide (CNO) significantly suppressed feeding. To evaluate the contribution of Pomc to this effect, 5-HT2CRCre:hM3Dq mice were pre-treated with the melanocortin4 receptor (MC4R) antagonist SHU9119, which prevented CNO-induced hypophagia. These findings provide new insight into the circuits engaged by 5-HT2CRs to impact food intake and suggest that the little studied population of NTS Pomc neurons play a role in 5-HT2CR appetite suppression.

Wellcome Trust (WT09801), BBSRC (BB/K001418/1), Diabetes UK (RD05/003059), the Juvenile Diabetes Research Foundation (1-2003-78; 1-2006-29) and NIH (DK066604; DK068400; DK056731).

Poster Ref: P3-E-011

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

Impaired gamma oscillations and diminished global EEG power in TASK-3 (kcnk9) knockout mice.

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TWIK-related acid-sensitive K^+ (TASK) channels are a subfamily of the tandem two pore potassium channel (K2P) family contributing to background potassium conductances. TASK-3 KO animals have disrupted sleep, with REM fragmentation and exaggerated wake consistently reported (Pang *et al.*, 2009; Steinberg *et al.*, 2014). In this study, we recorded electrocorticogram (EEG) and hippocampal local field potential (LFP) activity of TASK-3 KO and littermate control mice. In addition to supporting the earlier reports of disrupted REM and exaggerated wake, we found a global reduction in EEG power in KO animals including delta, theta, alpha, beta and gamma range activity throughout the sleep-wake cycle. Global hippocampal power was also affected during choice-making behaviour on a modified T-maze. Finally, when administered wake-promoting compounds, TASK-3 KO animals displayed an altered frequency composition in their EEG to that of controls, particularly in the gamma range.

References:

Pang, D.S., *et al.*, An unexpected role for TASK-3 potassium channels in network oscillations with implications for sleep mechanisms and anesthetic action. Proc Natl Acad Sci U S A, 2009

Steinberg, E.A., *et al.*, The role of K2P channels in anaesthesia and sleep. Pflugers Arch, 2014

Poster Ref: P3-E-012

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

Hypothalamic tanycyte signalling alter arcuate nucleus neurons activity..

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Hypothalamic tanycytes are glial cells lining the third ventricle of the mammalian brain. In rodents, they have been involved in various important hypothalamic functions such as the regulation of thyroid and sexual hormones or the local blood brain barrier. Recently, we demonstrated that these cells play an important role in sensing the concentration of nutrients such as glucose and amino acids in cerebrospinal fluid (CSF). Tanycytes send processes into the hypothalamic nuclei (arcuate nucleus, ventromedial hypothalamic nucleus) that control food intake and body weight. A key question is whether they are capable of communicating with neurons in these nuclei to pass on information about the nutrient levels in the CSF.

We have therefore created the first optogenetic tools to allow selective activation of tanycytes. We have expressed channelrhodopsin variants in tanycytes, to mimic the Ca^{2+} signals that arise during detection of nutrients in CSF. Optostimulation of tanycytes evoked depolarising potentials in neurons of the arcuate nucleus recorded with whole cell patch clamp. In many cases these depolarising potentials increased action potential firing. Optostimulation also increased the frequency of spontaneous excitatory synaptic potentials, suggesting that tanycytes act on many neurons within the hypothalamic networks. The arcuate nucleus contains neurons that express neuropeptide Y (NPY) and proopiomelanocortin (POMC), which respectively contribute to the orexigenic and anorexigenic pathways. Using a mouse line in which NPY positive neurons are marked with GFP, we showed that tanycytes excite these neurons. However, we also found that tanycytes excited POMC positive neurons and neurons of unknown chemical phenotype.

Our data are the first to demonstrate that tanycytes can signal to neurons to increase their excitatory synaptic inputs, to depolarize them and increase their firing. Further work is needed to elucidate the identities of the neurons that are activated by tanycytes and how this tanycyte-neuron communication could alter feeding behaviour.

Poster Ref: P3-E-013

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

Characterisation of the emergence of sleep disturbances in the unpredictable chronic mild stress murine model of major depression.

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There is growing evidence of a bidirectional relationship between sleep disturbances and major depression (MD), but this relationship remains poorly understood. Current antidepressants are only effective in one third of patients, and recent attempts to bring new drugs to market have failed. These fails are mainly due to a lack of valid translational models for MD. The aim of this study was thus to establish a translational murine model of sleep disturbances in MD in comparing the time-course of the emergence of sleep abnormalities to other depressive-like symptoms.

Adult BALB/c mice (18 weeks old) were subjected to a 9-week unpredictable chronic mild stress (UCMS) paradigm, consisting of daily exposure to social and environmental mild intensity stressors applied in a randomised way. The UCMS-induced physical, behavioural and endocrinal effects were compared with an undisturbed control group (n=9/group). Electroencephalogram/electromyogram (EEG/EMG) recordings were performed weekly (24-h recordings, 12-h light/dark cycle) to characterise the UCMS-induced changes in sleep architecture.

The UCMS paradigm induced a decrease of self-care and motivational behaviour respectively after 1 and 2 weeks of UCMS, which is characteristic of a depressive-like disorder. In addition, mice displayed alterations of the hypothalamic-pituitary-adrenal axis after 2 weeks of UCMS. EEG analyses showed an overall increase of total sleep time (TST) during the active (dark) period, as well as a decrease of TST during the sleep (light) period, after 5 weeks of UCMS. The UCMS also induced a substantial increase in rapid eye movement (REM) sleep appearing after 2 weeks of UCMS in both dark and light periods. Furthermore, the UCMS group displayed a decrease in non-REM sleep during the dark and light periods after 5 weeks of UCMS.

The current study suggests that the UCMS paradigm represents a promising translational model of the emergence of sleep disturbances in MD. Supplementary analyses are ongoing to further characterise the time-course of sleep alterations and other behavioural and neurochemical changes induced by the UCMS paradigm.

Poster Ref: P3-E-014

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

The role of gamma1 subunit-containing GABA-A receptors in sleep and temperature regulation in the preoptic hypothalamus.

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The preoptic area of the hypothalamus regulates core temperature and sleep (McGinty *et al.*, 1994; Alam *et al.*, 1995). It has neurones that are both warm-sensitive and active during the sleep phase. The γ1 subunit (gabrg1) of the GABA-A receptor is strongly expressed in the medial and median preoptic area, but in few other brain areas, suggesting that this receptor subtype has a special role in sleep and temperature regulation (Wisden *et al.*, 1992; Hörtnagl *et al.*, 2013). We designed shRNA to knockdown gabrg1 mRNA *in vivo* and stereotaxically injected C57BL/6 mice across the medial and median preoptic area, with adeno-associated virus expressing γ1 shRNA. Control mice were injected with a 'scrambled' sequence of non-targeting shRNA. We used the adrenergic alpha2 receptor agonist dexmedetomidine as a thermoregulatory challenge as it induces significant hypothermia as well as a sleep-like sedation. Drug dosing experiments, and sleep wake recordings, were performed in the home cage and filmed to quantify sedation. Further recordings were made using an activity monitor. At doses of 25 and 100 µg / kg IP, shRNA injected mice may have a deficiency in temperature regulation without correlated changes in sedation. This altered thermoregulation may extend into the sleep wake cycle.

Alam MN, McGinty D & Szymusiak R. (1995). Neuronal discharge of preoptic/anterior hypothalamic thermosensitive neurons: relation to NREM sleep. American Journal of Physiology 269, R1240-1249.
Hörtnagl H, Tasan RO, Wieselthaler A, Kirchmair E, Sieghart W & Sperk G. (2013). Patterns of mRNA and protein expression for 12 GABAA receptor subunits in the mouse brain. Neuroscience 236, 345-372.
McGinty D, Szymusiak R & Thomson D. (1994). Preoptic/anterior hypothalamic warming increases EEG delta frequency activity within non-rapid eye movement sleep. Brain Research 667, 273-277.
Wisden W, Laurie D, Monyer H & Seeburg P. (1992). The distribution of 13 GABAA receptor subunit mRNAs in the rat brain. I. Telencephalon, diencephalon, mesencephalon. Journal of Neuroscience 12, 1040-1062.

Poster Ref: P3-E-015

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

Differential sleep changes in normal and Batten disease affected sheep following sleep deprivation.

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Neuronal ceroid lipofuscinoses are a group of genetic neurodegenerative disorders commonly referred to as Batten disease. Pathology includes cortical and possibly thalamic degeneration; symptoms include motor deficits, blindness, mental retardation, seizures and sleep abnormalities.

We (Perentos *et al.*, in press) have shown that CLN5-/- Batten disease affected sheep (Frugier *et al.*, 2008) exhibit sleep abnormalities and abnormal electrophysiological signatures similar to the clinical features of Batten disease. These include reduced slow-wave amplitudes and spindles during NREM sleep.

Using the correlation of homeostatic sleep pressure with non-rapid eye movement (NREM) electroencephalograhy (EEG) delta power (0.5–4 Hz), we examined if slow-wave amplitudes can be increased in CLN5-/- sheep, or whether observed amplitudes represent maximal recruitment of neurons into the slow-wave oscillation. Using sleep deprivation, we manipulated the homeostatic sleep pressure and measured subsequent amounts of NREM sleep and delta powers.
At baseline, NREM sleep amounts were similar in affected CLN5-/- and control CLN5+/- sheep, whereas CLN5-/- sheep displayed significantly lower delta power and slow-wave amplitudes. This is consistent with previous findings in older CLN5-/- sheep (Perentos *et al.*, in press), and with reports of diminishing EEG amplitudes in patients during sleep and wakefulness. Following sleep deprivation, both groups displayed an identical increase in NREM sleep (~ 20% increase; $p < 0.05$). Control sheep displayed a two-fold increase in delta power after sleep deprivation but CLN5-/- sheep showed no delta power increase. These results suggest a relatively intact sleep homeostat in CLN5-/- sheep, but reduced ability to synchronously recruit thalamocortical and cortical neurons into slow-wave oscillations.

The study demonstrates that correlates of sleep pressure, as measured in humans and rodents, also apply to sheep, supporting the idea that sheep can be used to model human sleep.

Frugier *et al.*, CLN5 neuronal ceroid lipofuscinosis in Borderdale sheep. Neurobiol Dis 2008; 29: 306–15
Perentos N *et al.*, Translational neurophysiology in sheep: Measuring sleep and neurological dysfunction in CLN5 affected Batten disease sheep, Brain, in press

Poster Ref: P3-E-016

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

mir-1017 is a pleiotropic regulator of *Drosophila* sleep, locomotion and neurodegenerative phenotypes.

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Institute of Molecular and Cell Biology - Agency for Science, Technology and Research, Singapore

mir-1017 is a 3' tailed mirtron that lies within the intronic region of the *Drosophila* nAChRα2 gene and is highly enriched in the nervous system. We have established that mir-1017 knock-out mutants display hyperactivity, dysregulated sleep and accelerated neurodegeneration, which we replicated through expression of a mir-1017 sponge construct. Behavioural characterization in genotype-phenotype correlation analysis was performed with various mir-1017 *Drosophila* allelic combinations, including deletion alleles generated through targeted homologous recombination and deficiency lines. The host gene, nAChRα2, seems to be one of its regulated targets, governing basal locomotor activity as well as neurodegeneration, as probed by use of the *Drosophila* Activity Monitoring system and climbing assays respectively. RNAi knock down and overexpression studies of nAChRα2 rescued and phenocopied the behaviour accordingly, showing that overactivation of nAChRα2 as a result of mir-1017 absence is the likely cause of the defective physiology. Furthermore, we have disambiguated the sleep defects from the hyperlocomotion effects of the mutant phenotype. By using an enhancer fragment library, we show that mir-1017 can act in distinct neural circuits and that the sleep behaviours might in fact be regulated by a different mir-1017 target than its host gene. The pleiotropic nature and differential circuit expression of mir-1017 reflect the dynamic nature of microRNAs in flexible control of organism phenotypes. Thus, we have hereby uncovered mir-1017 as one of the molecular hubs controlling the fine regulation of various neuronal processes and their corresponding behaviours.

Poster Ref: P3-E-017

Theme: E: Sleep, Circadian and Neuroendocrine Mechanisms

Validation of infrared thermography as a method of assessing the circadian rhythm of body temperature in mice.

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Body temperature is traditionally measured by contact methods, inserting probes into the rectum or external ear canal to achieve a reading approximating that of the body core. Measuring the core temperature of conscious animals requires restraint which is potentially stressful and may induce pyrexia which confounds scientific data quality. Mice are the most commonly used biomedical research model and their body temperature shows a clear circadian rhythm which is associated with, but not entirely dependent on locomotor activity. Measuring the temperature of mice typically requires surgical implantation of telemetry devices, and this has limited its use as a physiological output marker in circadian studies.

Infrared thermography (IRT) or thermal imaging measures the radiant heat emitted from the body surface and has been used in human and veterinary medicine to detect localised areas of inflammation or increased blood flow. Previous studies comparing IRT to other methods of temperature assessment have delivered inconsistent results- one reason may be that the relationship between core and peripheral temperature was not quantified or accounted for. A thermal camera used routinely in industrial processes can track a mouse's peripheral hotspot (usually on the face, a well-vascularised area) by imaging from above, through a conventional wire cage lid. A commercially-available radiotelemetry implant was placed intraperitoneally and both core and peripheral temperatures were recorded longitudinally over several days and under different ambient light cycles. Peripheral body temperature was found to be around 3°C lower than core, as expected and a stable relationship was demonstrated between the two absolute values which persisted throughout the daily cycle (Figure 1). The non-invasive nature of IRT delivers data free from stress-induced artefacts and improves animal welfare and has further potential in circadian phenotyping, in post-operative and infectious disease monitoring situations and following dosing in regulatory toxicology studies.

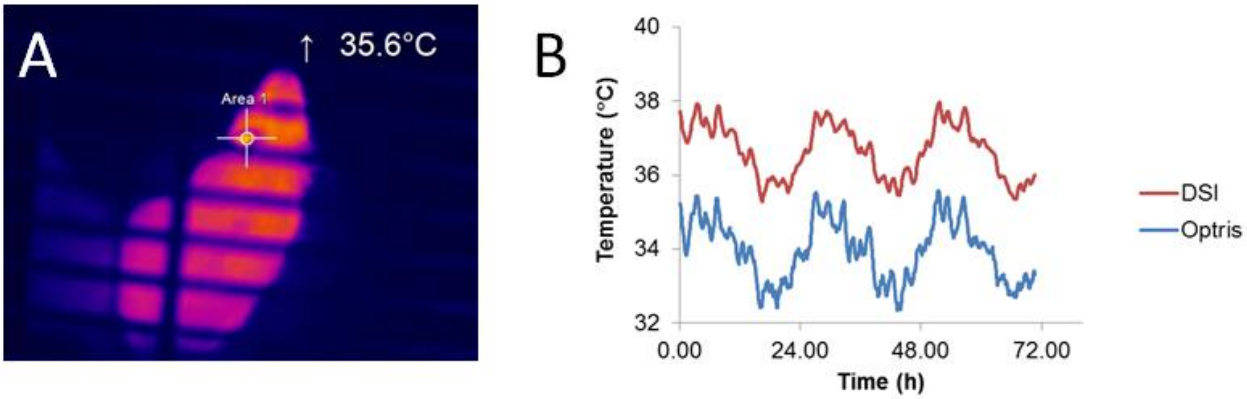

Figure 1. Thermal image of mouse with hotspot, Area 1 detected around the eye (A) and plot of body temperature against time, measured by both DSI telemetry and Optris thermal camera, showing a clear circadian rhythm and ultradian changes associated with locomotor activity (B).

Theme F: Nervous System Disorders

Posters P3-F-001 to P3-F-058

Poster Ref: P3-F-001

Theme: F: Nervous System Disorders

Are there neuroprotective properties in the parvopyramidal layer of the presubiculum that could prevent degeneration?

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Introduction: Previous findings show that the parvopyramidal layer of the presubiculum accumulates amyloidogenic proteins in a range of diseases, but only minimal neurofibrillary degeneration is seen. However, in the neighbouring entorhinal cortex and subiculum severe neuronal loss and deposition of amyloid plaques is observed. Alzheimer's disease (AD), familial British dementia (FBD) and familial Danish dementia (FDD) all share common pathological hallmarks of amyloid deposits and neurofibrillary tangles. Using post-mortem brain samples from these neurodegenerative diseases, we aim to characterise the protein deposits and determine the level of microglial activation in both the parvopyramidal layer of the presubiculum and the neighbouring areas. By doing this we hope to determine if these cells have protective properties from degeneration.

Materials and Methods: Immunohistochemistry was performed on cases of AD, FBD and FDD in order to visualise the parvopyramidal layer of the presubiculum. Frozen sections were stained and both the parvopyramidal layer and amyloid plaques from the entorhinal cortex were laser captured for biochemical analysis of the amyloid peptides. Microglial activation was also investigated in the parvopyramidal area and compared to the entorhinal cortex.

Results: The protein deposits found in the parvopyramidal layer were not accompanied by neurofibrillary tangles (NFTs) or neuropil threads (NTs) which were observed in the entorhinal cortex in AD, FBD and FDD. A marked reduction in microglial activation was observed in the parvopyramidal layer compared with the entorhinal cortex.

Conclusion: We have shown that in AD, FBD and FDD, the parvopyramidal region contains diffuse deposits of amyloidogenic proteins without NFT or NT formation and with minimal microglial activation. Understanding why this region has a different pathology to neighbouring areas may provide further insight into the disease mechanisms.

Poster Ref: P3-F-002

Theme: F: Nervous System Disorders

Focal triphasic sharp waves and spikes in the electroencephalogram.

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Introduction: There is a plethora of data in the EEG literature on the characteristics of the most prominent component of interictal epileptiform discharges (IED), namely the negative (fast) phase. Surprisingly, however, little attention has been drawn to the after-coming slow wave (ASW), and its pathological as well as clinical significance. In this paper, we will address the significance of prominent (high amplitude) ASW, giving rise to a triphasic morphology of the IED (focal triphasic sharp waves and spikes-FTSW). We will discuss this EEG pattern with respect to its clinical, neurophysiological, and neuropathological significance.

Method: This investigation was conducted on a heterogeneous group of patients at KKH, Ha'il, KSA.

Result: Our data revealed that FTSW were rare EEG events occurring primarily in the first two decades of life. Ninety percent of the patients with FTSW had epilepsy, presenting clinically with generalized convulsive seizures, often without partial onset. The majority of these patients responded favorably to anticonvulsant monotherapy. We were surprised to find that half of the patients with FTSW had chronic and/or static CNS pathology, particularly congenital CNS anomalies.

Conclusion: Even though more than one mechanism may be involved in the pathogenesis of FTSW, we believe a deeply seated pacemaker as the source of this EEG pattern is the most compelling theory. The presence of FTSW should alert clinicians to the possibility of an underlying chronic and/or static CNS pathology, in particular congenital CNS anomalies, underscoring the significance of neuroimaging in the work-up of this population. Moreover, it is conceivable that the prominent ASW may contribute to the interictal intellectual dysfunction of these patients, justifying aggressive anticonvulsant therapy.

Poster Ref: P3-F-003

Theme: F: Nervous System Disorders

Positive sharp waves in the EEG of children and adults.

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Introduction: Interictal epileptiform discharges (IEDs) with negative polarity have been extensively studied in the EEG literature. However, little attention has been drawn to IED with positive polarity [positive sharp waves (PSWs)]. In this paper, we discuss pathophysiological, neuroimaging, and clinical correlates of this pattern in a heterogeneous group of children and adults who demonstrated PSW in their scalp EEG.We documented EEG parameters as well as demographic, clinical, and neuroimaging data.

Method: We prospectively reviewed the EEGs of 1,250 patients from a heterogeneous population over a period of 1 year. Statistical analysis was performed to correlate the aforementioned data.

Result: Thirty-one patients had PSW in their EEG.The analysis showed that PSW is an epileptogenic pattern with localizing significance, occurring primarily in the younger age groups. Furthermore, there was a strong association of PSW with chronic and/or static CNS pathology, in particular, congenital CNS anomalies, often accompanied by psychomotor retardation. Patients with "multifocal" PSW invariably exhibited severe intellectual and motor deficits associated consistently with a variety of congenital CNS insults.

Conclusion: PSW is a rare and under-reported EEG abnormality which, similar to negative IED, signifies focal epileptogenecity. The presence of PSW should prompt neuroimaging studies to investigate an associated chronic/static CNS pathology, in particular, congenital CNS anomalies. This association is particularly strong when PSW is multifocal in which case patients present with severe intellectual and motor deficits.

Poster Ref: P3-F-004

Theme: F: Nervous System Disorders

Salience and reward prediction error abnormalities in people with first episode of psychosis and at risk mental states.

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There is evidence of reinforcement learning abnormalities in people with psychosis. Reinforcement learning promotes learning stimulus–outcome associations and is driven by prediction error. Our aim was to investigate the involvement of fronto-striatal circuitry during reinforcement learning and its disruption with the emergence of early psychotic symptoms. During the fMRI scan, people at risk for developing psychosis (ARMS, n= 25), patients with first episode of psychosis (FEP, n = 17) and healthy volunteers (n = 33) performed an instrumental learning task involving monetary gains. We examined the brain activity participants during two contrasts. The first one, salience, compared physiological responses while looking at bivalent cues (cues that have a 50% chance of winning or losing £1) minus looking at neutral cues. The second contrast, prediction error, was the difference in the outcomes of winning £1 in bivalent *vs*. reward trials.

All of the participants learned which pictures led to reward, and chose those pictures more often. We observed an attenuated striatal response to salient stimuli and an augmented response to neutral stimuli in people with psychosis. Increased striatal activity in response to neutral stimuli in patients with ARMS was correlated with the severity of their psychotic symptoms. In both patient groups, more severe psychotic symptoms were associated with lower activity in the left frontal pole during the salient *vs*. neutral contrast. In the ventral striatum, middle frontal and paracingulate gyri, patients with FEP had less activity during prediction error than controls or patients with ARMS, whereas there was no significant difference between healthy volunteers and patients with ARMS.

Our study demonstrated that patients with FEP have abnormal brain activity during reinforcement learning in a fronto-striatal network that is driven by increased responses to neutral stimuli and decreased responses to reward prediction error. In addition, in patients with ARMS there is an important link between psychotic symptoms and their striatal responses to neutral cues, which is consistent with the aberrant motivational salience hypothesis. Our findings provide evidence of aberrant neural processing of salience and prediction errors in psychosis.

Poster Ref: P3-F-005

Theme: F: Nervous System Disorders

Lennox-gastaut syndrome associated with dysgenesis of corpus callosum.

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Introduction: Lennox-Gastaut syndrome(LGS) is an electro-clinical syndrome composed of the triad of mental retardation, multiple seizure types, and the characteristic generalized slow spike-wave complexes in the EEG. In this article, we report on two patients with LGS whose brain MRI showed dysgenesis of corpus callosum(CC). We review the literature and stress the role of CC in the genesis of secondary bilateral synchrony(SBS).

Method: This was a clinical study conducted at King Khalid Hospital.

Results: The EEG was consistent with LGS in patient 1 and unilateral slow spike-wave complexes in patient 2 . The MRI showed hypoplasia of the splenium of CC in patient 1, and global hypoplasia of CC combined with Joubert syndrome in patient 2.

Conclusion: Based on the data, we proffer the following hypotheses :
1-Hypoplasia of CC interferes with functional integrity of this structure.
2-The genu of CC plays a pivotal role in the genesis of secondary bilateral synchrony.
3-Electrodecremental seizures in LGS emanate from pacemakers generated in the brain stem, in particular the mesencephalon projecting abnormal signals to the cortex *via* thalamic nuclei.
4-Unilateral slow spike-wave complexes in the context of mental retardation and multiple seizure types may represent a variant of LGS,justifying neuroimaging studies.

Poster Ref: P3-F-006

Theme: F: Nervous System Disorders

Lymphotactin (XCL1) modulation of trigeminal subnucleus caudalis (Vc) excitability *in vitro*.

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[1]School of Biomedical Sciences, University of Leeds, [2]School of Medicine, Pharmacy and Health, University of Durham, [3]Department of Oral and Maxillofacial Medicine and Surgery, University of Sheffield

Pro-inflammatory cytokines are implicated in chronic pain and processes linked to central sensitization through mechanisms that have not been fully elucidated yet. Lymphotactin (XCL1) signals *via* the receptor XCR1 but its role in modulation of excitability and central sensitization is unknown. In this study, we hypothesize a contribution of XCL1 to central sensitization in the trigeminal subnucleus caudalis (Vc), an area linked to oro-facial pain. In this study, immunohistochemistry was used to investigate if XCL1 can activate *in vitro* the immediate early gene c-fos and members of the Mitogen-Activated Protein Kinases (MAPK) family, namely phosphorylated P38 (p-P38) and phosphorylated extracellular signal-regulated kinase (p-ERK) which are known to be involved in mechanisms of central sensitization. Electrophysiology in rat trigeminal brainstem slices *in vitro* was used to determine the effects of XCL1 on Vc excitability. All procedures were carried out under anaesthesia (pentobarbital, 50 mg/kg i.p.) and accorded with UK Home Office legislation.

Incubation of trigeminal brainstem slices with XCL1 (2h) resulted in an increased activation of c-fos, p-P38 and p-ERK in the superficial layers of Vc, as assessed by semi-quantification of immunostaining ($p < 0.0001$, $p < 0.01$ and $p < 0.001$, respectively). XCL1-induced activation of these markers was blocked by the XCR1 antagonist vMIP-II. Extracellular recordings were made in Vc using transverse brainstem slices. Superfusion with XCL1 (2h) enhanced a form of rhythmic activity that can be quantified using spectral analysis. XCL1 significantly increased power area and power amplitude parameters ($p < 0.05$) indicating an enhanced level of intrinsic excitability. This is similar to 4-aminopyridine-induced augmented excitability in spinal cord which has been used as a model of enhanced central excitability. XCL1-induced increase in intrinsic excitability was blocked by vMIP-II. These data reveal that XCL1 modulates central excitability and activation of specific markers of central sensitization within a key area of the trigeminal brainstem that is involved in modulation of nociceptive signals and suggest a possible role for this chemokine in the pathogenesis of chronic trigeminal oro-facial pain.

Research funded by BBSRC as an Industrial Partnership award with Pfizer, UK.

Poster Ref: P3-F-007

Theme: F: Nervous System Disorders

Mouse xenograft model of corticospinal tract by delayed transplantation of olfactory ensheating cells in adult rats.

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Adult rats were trained to use their forepaw for retrieving a piece of noodle through a slit in the front of the cage. The dorsal corticospinal tract was lesioned by a focal stereotactic radio-frequency lesion at the level of the first/second cervical segment. Complete destruction of one side of the corticospinal tract completely prevented the use of the ipsilateral forepaw reaching for at least 6 months after operation. Rats which have shown no forepaw retrieval by 8 weeks were xenotransplanted with a suspension of cultured olfactory ensheathing cells derived from the mouse olfactory bulb, into the lesion site. Starting between 1 and 3 weeks, 10 rats with transplants bridging the lesion site resumed ipsilateral forepaw reaching.The histology of the lesioned rats with misplaced olfactory ensheathing cell showed no functional recovery during the 8 weeks of training.

Poster Ref: P3-F-008

Theme: F: Nervous System Disorders

Neuroprotective and behavioural effects of mglur8 agonist DCPG in the lactacystin and LPS models of Parkinson's disease.

David Dexter and Claire Williams

Imperial College London

Objective: Ascertain the neuroprotective/behavioural effects of targeting metabotropic glutamate receptor subtype 8 (mGluR8) in the lactacystin and LPS rat model of Parkinson's utilising the agonist (S)-3,4-dicarboxyphenylglycine (DCPG).

Background: Excess glutamatergic signalling in the basal ganglia and neuroinflammation are features of neurodegenerative process in Parkinson's. Evidence suggests that pharmacological activation of the mGluR4 subtype can provide significant neuroprotection and reduce behavioural deficits in traditional toxin rodent models of Parkinson's by reducing neuronal excitability. However, it is not known whether targeting mGluR8 can trigger similar effects.

Methods: Rats were unilaterally lesioned with the proteasome inhibitor lactacystin or Lipopolysaccharides (LPS) in the substantia nigra (SNc).DCPG was administered systemically for 14 days starting 4 days after lactacystin lesioning and for 7 days starting the next day after LPS lesioning. Forelimb-use asymmetry tests and amphetamine-induced rotations were used to assess behavioural deficits, whilst immunohistochemistry and stereological quantification of SNc dopaminergic neurons and microglia was performed.

Results: DCPG treatment was associated with a small neuroprotective effect on the loss of dopaminergic neurons in both the lactacystin (~10% neuroprotection) and LPS (~24% neuroprotection. This was associated with a small attenuation in forelimb-use asymmetry but not in amphetamine-induced rotations in both models. DCPG treatment was also associated with a modest but not significant reduction in SNc microglial activation in both models.

Conclusion: Although the mGluR8 agonist DCPG did induce neuroprotection in both animal models the degree of neuroprotection was too small to support the concept that targeting mGluR8 receptors are a worthwhile neuroprotective target for treating Parkinson's.

Poster Ref: P3-F-009

Theme: F: Nervous System Disorders

Neuroprotective effects of delayed start administration of the class III HDAC inhibitor nicotinamide in the lactacystin model of Parkinson's disease.

David Dexter and Ian Harrison

Imperial College London

Objective(s): Determine whether the class III pan-HDAC inhibitor nicotinamide is neuroprotective in the lactacystin model of Parkinson's using a delayed start treatment model.

Background: Epigenetic changes, both DNA methylation and histone modification, occur in the Parkinson's brain. It has been hypothesised that histone hypoacetylation through overactivity of histone deacetylases (HDAC's) leads to chromatin condensation and repression of gene expression leading to neuronal death. Hence, HDAC inhibitors (HDACI's) have been proposed as neuroprotective agents. Nicotinamide, a naturally occurring substance well tolerated by humans, a pan HDAC class III (Sirtuins) inhibitor and has been demonstrated to protect against MPTP toxicity when given as a pre-treatment which does not mirror the potential clinical setting.

Methods: 250mg/kg or 500mg/kg nicotinamide was administered i.p. for 28 days starting 7 days after the induction of a lactacystin lesion to the substantia nigra (SNc). Forepaw-use asymmetry, amphetamine induced rotations, MRI brain scans was assessed at baseline and weekly during the study. At the end of the study SNc dopaminergic neuronal counts were performed by tyrosine hydroxylase immunohistochemistry/stereological counting. RT-PCR was utilised to assess gene expression.

Results: Despite nicotinamide reversing the lactacystin induced histone hypoacetylation and stimulating gene expression of glial derived neurotrophic factor (GDNF) and the anti-apoptotic factor Bcl2, nicotinamide failed to induce any neuroprotective effects when assessed by MRI, behaviour or *via* SNc dopaminergic neuronal counts.

Conclusions: Unlike the pan-class I/IIa HDACI valproate the pan-class III HDACI nicotinamide is not neuroprotective in the lactacystin model of Parkinson's suggesting pan-inhibition of Sirtuins is not neuroprotective.

Poster Ref: P3-F-010

Theme: F: Nervous System Disorders

Parkinson's UK Tissue Bank: A unique tissue resource for Parkinson's research.

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Imperial College London

Background: Parkinson's UK Tissue Bank was established in 2002 to collect and supply high quality human brain, spinal cord, DNA and CSF samples to researchers. Tissue is collected through a donor programme with almost 10,000 potential donors. To date we have collected almost 800 Parkinson's related brains and we are currently collecting ~110 cases per year with short post-mortem delays. Neuropathological examination utilise the latest international criteria, are graded according to Braak along with the degree Alzheimer's type co-pathology. Extensive medical histories exist on all cases.

Objectives: To act as an open access tissue resource for researchers so as to foster research towards a better understanding/cure for Parkinson's. We have supplied tissue to hundreds of key research projects *e.g.* GWAS sequencing project. A number of different tissue formats are available i.e. snap frozen, formalin fixed - paraffin embedded, and formal fixed – cryopreserved tissue.

Access: The Tissue Bank welcomes applications from both for profit and not for profit organisations. Tissue request forms can be requested *via* the tissue bank manager, all applications are reviewed by an independent scientific review board. The Tissue Bank *via* its review board can issue its own ethical approval for the use of tissue, under the MREC scheme, thus saving the need for researchers to get separate ethical permission in many cases.

Poster Ref: P3-F-011

Theme: F: Nervous System Disorders

Investigating disease mechanisms and biomarkers for Alzheimer's Disease in people with Down Syndrome: a study of mitochondrial dysfunction.

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The development of treatments aimed at preventing dementia in people with Down syndrome (DS) requires an understanding of disease mechanisms and, as potential treatments are developed, their testing will depend upon the use of early and sensitive clinical and cognitive indicators for developing dementia and also of early biomarkers for Alzheimer's disease (AD). Previous research has suggested that behavioural changes and measures of executive function (EF) are early indicators of developing dementia that precede memory decline. We report on a systematic literature review and on an analysis of cognitive and behavioural findings from a study of people with DS using structural MRI and [11C]-PiB-PET neuroimaging. Mitochondrial dysfunction has been observed in Down Syndrome and contributes to accelerated aging. We present data on *in vivo* measures of mitochondrial function in muscle and their association with the above cognitive measures.

So far, 51 participants with DS (mean age 41.71, range 30-56) have had MRI and PET scans and completed comprehensive assessments of EF and memory. Deteriorations in personality and behaviour were quantified from changes reported in the CAMDEX-DS informant interview and categorized into excesses and deficits. A subset of participants is currently undergoing MRS scans of post-exercise Phosphocreatine (PCr) recovery time, as a measure of mitochondrial dysfunction.

Initial analyses suggest that reported changes in behaviour and impaired performance on measures of EF can differentiate between participants with and without a diagnosis of dementia. In contrast, no significant differences were identified on tests of memory, suggesting that, although these are sensitive to early signs of AD in the general population, they are unlikely to be useful in the early diagnosis of DSAD. In this study we will explore the relationship between different cognitive and behavioural data with measures of mitochondrial dysfunction and PET and MRI neuroimaging findings. Identifying measures that are sensitive to the very early signs of impending dementia consequent upon particular neuropathology and dysfunctional energetics will contribute to our understanding of the progression of DSAD and may improve treatment outcomes by facilitating early interventions.

Poster Ref: P3-F-012

Theme: F: Nervous System Disorders

Roles of endothelin-1 in beta-amyloid-induced neurotoxicity in hippocampus: An implication for Alzheimer's pathology.

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Alzheimer's disease (AD) is an incurable neurodegenerative disorder. Abnormal levels of endothelin-1 (ET-1) have been demonstrated in parietal white matter(1), cerebral cortex and vessels of the AD brain(2). Neuronal death and accumulation of beta-amyloid (Aβ) are prominent pathological features of AD. Significant neuronal death is found in Aβ-treated primary neurons and Aβ-overexpressing mouse models(3,4). ET-1 is a known vasoconstrictor and neuro-active peptide. ET-1 induces apoptosis in primary retinal neurons(5). In contrary, ET-receptor (ETR) type B agonist can rescue neurons from Aβ-induced apoptosis(6). These findings suggest ET-1 plays dual roles in neurodegeneration and neuroprotection, respectively. This study aims to investigate the effect of ET-1 on Aβ-induced cell death in hippocampal neurons.

Primary hippocampal neurons were pretreated with or without ETR antagonists prior to the treatment of oligomeric form of Aβ1-42, ET-1 or both on 14 DIV. Cell viability was measured by MTT assay. Changes in protein expression in apoptotic and ET-1 signaling pathways were assessed by western-blot analysis. This study shed light on the roles of ET-1 in Aβ1-42-neurotoxicity, building upon which the ET-1 signaling pathway as a potential therapeutic target for AD can be further investigated.

1.Barker, R., *et al.*, Pathophysiology of white matter perfusion in Alzheimer's disease and vascular dementia. Brain, 2014. 137(Pt 5): p. 1524-32.
2.Minami, M., *et al.*, Endothelin-1-like immunoreactivity in cerebral cortex of Alzheimer-type dementia. Prog Neuropsychopharmacol Biol Psychiatry, 1995. 19(3): p. 509-13.
3.Wirths, O. and T.A. Bayer, Neuron loss in transgenic mouse models of Alzheimer's disease. Int J Alzheimers Dis, 2010. 2010.
4.Deshpande, A., *et al.*, Different conformations of amyloid beta induce neurotoxicity by distinct mechanisms in human cortical neurons. J Neurosci, 2006. 26(22): p. 6011-8.
5.Oku, H., *et al.*, Endothelin-1 (ET-1) causes death of retinal neurons through activation of nitric oxide synthase and production of superoxide anion. Exp Eye Res, 2008. 86(1): p. 118-30.
6.Yagami, T., *et al.*, Effects of endothelin B receptor agonists on amyloid beta protein (25-35)-induced neuronal cell death. Brain Res, 2002. 948(1-2): p. 72-81.

Poster Ref: P3-F-013

Theme: F: Nervous System Disorders

VPA attenuates beta-amyloid-induced dysfunction in synaptic transmission in rat primary neurone cultures.

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Alzheimer's disease (AD), a debilitating progressive neurodegenerative disorder and the most frequent and common form of dementia in the elderly (>60 years old), is placing alarming pressure on healthcare systems globally. Although the precise aetiology of the AD is still a subject of debate, it is generally believed that synaptotoxic effects of soluble Aβ oligomers trigger the onset of the disease, inducing early brain circuity defects that over the years develop into AD. Thus, a lot of effort is being put into understanding the early asymptomatic stages induced by Aβ. We have previously shown that exposure of neurons at low concentration of Aβ oligomers modulate neurotransmitter (NT) release by interfering with the interaction of synaptic vesicle (SV) proteins. Here we demonstrate a novel mechanism by which Aß induces defective neuronal activity through disrupting the phosphorylation pattern of Synapsin I, a protein that regulates the number of SVs available for NT release. In addition we also show that treatment with Valproic acid (VPA) attenuates this effect. A brief application of either high or low concentrations of oligomeric Aß42 to cultured primary rat neurones, is followed by its internalisation and localisation to the presynaptic contacts. Interestingly, although high concentrations of Aß42 disrupts the phosphorylation/de-phosphorylation regulation of serine 9 residue of Synapsin I, low concentrations of Aß42 do not have a significant effect. Moreover, co-treatment of cultured neurones exposed to high concentrations of Aß42 with VPA, significantly attenuates this effect.

These results suggest a unique and interesting mechanism for Aß-induced neuronal dysfunction, an early event in AD pathogenesis, but importantly we also provide evidence of a mechanism of action of VPA in blocking this effect. Our data suggests that elucidating the targets of Aß at the synapse and inhibiting these effects may be key in developing preventive and disease modifying therapeutic strategies to combat neuronal damage and thus cognitive decline in AD.

Poster Ref: P3-F-014

Theme: F: Nervous System Disorders

Optimisation of AAV gene therapy in a mouse model of Rett syndrome: a dose escalation study.

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Rett syndrome (RTT) is a neurological disorder characterized by impairment of motor and cognitive functions and affecting almost exclusively females. Typical RTT is caused in almost all cases by *de novo* mutations in the X-linked gene, MECP2. Studies in mice suggest that reactivation of a silenced Mecp2 allele can reverse and prevent RTT-like neurological deficits. We and others have demonstrated the effectiveness of viral-based gene therapy approaches in improving aspects of the RTT-like phenotype in knockout mice. Nevertheless, there are many variables to consider for translational application, including vector design, dosage, route and age of delivery. The aim of this study was to find out the optimal dosage of transgenic MeCP2 using a self-complementary AAV9 vector.

A human MECP2 minigene was cloned as a fusion with a Myc epitope tag under the control of a fragment of the Mecp2 endogenous core promoter (MeP). This construct was flanked by AAV2 ITR elements and used to generate self-complementary (sc) AAV9 virus particles. Viral particles (ranging from 10e11 to 10e13 vg/mouse) were injected intravenously into 4-5 week old wild-type and knockout (Mecp2-/y) mice. Exogenous MeCP2 expression was detected in the brain of injected mice with dose- and brain region-dependent transduction efficiency (0.5-1% of cells transduced after the lowest dose and 12-20% after the highest dose). High transduction levels were observed in the liver, resulting in dose-dependent histopathological changes. No therapeutic benefit, in terms of amelioration of RTT-like features, was observed after administration of 10e11 vg/mouse compared to the control, whereas injection of 10e13 vg/mouse was associated with toxicity. Several intermediate doses and different vector designs are currently under investigation. Our data thus far clearly show that vector dosage is an important factor in determining both therapeutic success and the probability of adverse events, and will influence the design of translational studies of gene therapy in RTT.

Poster Ref: P3-F-015

Theme: F: Nervous System Disorders

Purkinjec cell degeneration (pcd) 5J mutant mice: A quantitative, morphological and immuohistochemical study of Bergmann glia and Purkinje cells.

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In mouse, the Purkinje cell degeneration (pcd) is an autosomal recessive neurodegenerative disease caused by mutation in Nna-1 gene. PCD mice are characterized by a rapid degeneration of Purkinje cells (PCs) between the third and fourth weeks of age leading to ataxia. Evidence from the literature suggests that Bergmann glia (BG), radial glial cells in the Purkinje cell layer proliferate in response to this injury causing Bergmann gliosis. In this study, we analysed Bergmann glial cells and their fibres immunohistochemically in postnatal pcd 5J mice (P17, 21, 26, and 100). At P17, both control and homozygous pcd tissues showed similar immunostaining pattern. At P21, a patchy loss of PCs was observed which progressed rapidly at P26, and by P100 no PCs were present in the cerebellum but there was an increase in BG number. This was followed by histological and morphological changes of the molecular and granular layer in P100 tissue. In order to assess the astrocytic response to this pathology, we analysed GFAP expression and noticed that BG fibres lost their uniform appearance and distribution as long parallel fibres across the molecular layer at day 26, and by P100, BG fibres became disorganized, thicker with intense GFAP staining. Increased numbers of GFAP positive astrocytes were also noticeable in the molecular layer suggesting that pcd induces astrocytes activation in the cerebellum. Furthermore, we were able to isolate neural stem cells from homozygous pcd 5J and wild type mice at P21. These results suggest that BG is involved in pcd pathology of adult mouse cerebellum, and characterisation of neural stem cells from ataxic mice will help for the development of future therapies for brain repair.

Poster Ref: P3-F-016

Theme: F: Nervous System Disorders

Genetic determinants of swallowing symptoms related to dysphagia in a healthy older adult cohort.

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University of Manchester

Introduction: Patients with swallowing difficulties (oro-pharyngeal dysphagia) caused by neurological damage (stroke, Parkinson's disease, ageing) show different recovery patterns which may be caused by genetic determinants. The aim is to find an association between human genetic variations and swallowing impairments within the ageing cohort.

Materials and methods: We performed case-control genome wide association study (GWAS) of self-reported swallowing symptoms related to dysphagia. The analysis included 555 community dwelling, unrelated, older adults (mean years of age = 81.4; SD = 5.349) with known phenotype and genetic information consisting of 512 806 single nucleotide polymorphisms (SNP). Gene-based association analysis of these traits was also conducted. The genetic data underwent quality control procedures prior to the study. This included analysis of population architecture using Multidimensional Scaling of the genome-wide genotype data.

Results: Analysed cohort showed European ancestry with no major population stratification. The results shown one genome wide significant SNP rs17601696 (P=4.83x10-8) from non-coding region of chromosome 10. Analyses of individual genes did not result in any genome-wide significant association.

Discussion: SNP rs17601696 may have an impact in swallowing impairment among elderly individuals. The results require replication in an independent cohort with appropriate phenotype/genotype data. Presented GWAS results will be replicated in the human model study using Transcranial Magnetic Stimulation (TMS). Identified genetic loci may play a role of potential markers to predict individual's outcome from swallowing impairments.

Poster Ref: P3-F-017

Theme: F: Nervous System Disorders

Autonomic consequences of spontaneous temporal lobe epileptic seizures.

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Sudden unexpected death in epilepsy (SUDEP) is a constant threat to people with epilepsy; the overall risk of dying unexpectedly is >20% higher than the general population and for people with chronic refractory epilepsy SUDEP has been reported to account for up to 50% of deaths (2). Epileptic seizures are accompanied by autonomic disturbances, including cardio-respiratory abnormalities (1). Little is known about the long-term effects of repeated episodes of autonomic dysfunction but it is possible that repeated seizure activity predisposes to the development of a fatal seizure-induced autonomic event.

In the present study we carried out long term monitoring of the cardiac activity in a rat model of temporal lobe epilepsy (3) to investigate whether seizure-related cardiac changes were affected by seizure history. Focal microinjections of tetanus neurotoxin (TeNT) were made into the ventral hippocampus in male Wistar rats, instrumented to record cortical EEG and ECG (lead II) by radiotelemetry. TeNT induced repeated spontaneous brief (20-140 s) seizures, often in clusters, and recurring over weeks.

>95% of seizures were associated with prolonged tachycardia, lasting <53 min, long after each seizure had ended. Dysrhythmias and bradycardias occurred during ~90% of seizures: a minority had sinus bradycardia alone, while in most cases bradycardia included episodes of asystole, premature ventricular depolarisations and fibrillation. Episodes of disrupted heart activity could last 10-20 s. The incidence, intensity and duration of these seizure-related changes in cardiac activity varied considerably over the course of each rat's epileptic syndrome. Secondarily generalized seizures (4-5 on the "Racine Scale") and seizure clusters both were associated with increases in tachycardia and with more prominent dysrhythmias.

Understanding the cardiac and respiratory consequences of repeated epileptic seizures will provide rational approaches to predicting and reducing the risk of SUDEP.

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1. Massey CA *et al.* (2014) Nature Rev Neurol 10: 271-282
2. Shorvon S & Tomson T (2011) Lancet 378: 2028-38
3. Jiruska *et al.* (2010) Brain 133:1380-90

Poster Ref: P3-F-018

Theme: F: Nervous System Disorders

Neurochemical measurements in the zebrafish brain: using fish models to understand the neurochemistry of aggression.

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Aggression is an important adaptive behaviour that animals use to fight for resources, protect offspring and establish dominance hierarchies. Our laboratory uses zebrafish (*Danio rerio*) to study the genetic, neurological and pharmacological control of aggressive behaviour. As well as making measurements in wild type fish, we have been characterising the alterations to neurotransmitter release and global brain activity in mutant lines that show increases or decreases in aggression. High performance liquid chromatography (HPLC) analysis of brain homogenates taken from four different brain areas (forebrain, optic tectum, hypothalamus, hindbrain), has shown regional differences in amine (dopamine, noradrenaline, serotonin and histamine) and amino acid (glutamate, GABA) levels in wild type fish brains. Moreover, in the parade mutant, a low-aggression mutant zebrafish, levels of serotonin were found to be reduced across all brain regions. In parallel, we have established fast cyclic voltammetry (FCV) in zebrafish brains *in vitro*, permitting the real time measurement of extracellular neurotransmitter levels in localised brain regions. Our data show the characteristic oxidation and reduction profiles of dopamine, serotonin and histamine, and pharmacological verification suggests that we can indeed separate all three amines in the brains *in vitro*. Potassium-stimulated release of all three amines has been measured in six different brain areas, and the data demonstrate differences in stimulated release between brains of wild-type and parade mutant fish. Neurochemical measurements in these fish models help elucidate neural mechanisms underlying aggression, which will be beneficial to understanding aggressive behaviour in people.

Poster Ref: P3-F-019

Theme: F: Nervous System Disorders

Transcriptional changes as a result of learning and aging in the HdhQ150 mouse model of Huntington's disease.

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Transcriptional changes are an early pathological event in Huntington's disease (HD). Significant changes in gene expression have been reported in the brains of mouse models of HD that are similar to transcriptional alterations seen in human HD brain and that correlate with deficits in motor, learning, and memory tasks. However, learning itself affects gene expression, thus we aimed to investigate what effect this might have on brain gene expression in HD mouse models. In a cohort of knock-in HdhQ150/+ and wild-type (WT) mice, we performed an experimental series based around the serial implicit learning task (SILT) to examine gene expression changes that may contribute to, or be dependent upon, learning. To investigate gene expression differences associated with learning we used three cohorts of mice: 1) untrained; 2) simple (FR1) acquisition training or 3) extensively trained on the SILT. To investigate whether potential gene expression changes associated with learning were age-dependent, we examined HdhQ150/+ and WT animals that had undergone the different levels of SILT training at 3 or 6 months of age. Gene expression profiles were generated using GeneChip® Mouse Gene 2.0 ST Array chips (Affymetrix, California, USA) and analysed through a standard pipeline. Changes in expression of genes implicated in cognition were evident in both genotypes (DAVID enrichment "Vesicle-Mediated Transport"; WT: $p = 1.88x10-03$; HdhQ150/+: $p = 3.66x10-04$; all p=values were false-discovery rate adjusted). mRNAs associated with protein transport were found to be significantly enriched over time in both HdhQ150/+ ($p = 6.85x10-05$) and WT animals ($p = 5.18x10-09$), with WT animals also showing significant enrichment in mRNAs associated with chromatin acetylation ($p = 4.07x10-07$). Notably, animals that had undergone behavioural training at 6 months of age showed a transcriptional profile more closely resembling that of both untrained and trained 3 month old animals, than those that were untrained at 6 months of age. Our results provide evidence for age- and learning-related differences in the transcriptional profile of WT and HdhQ150/+ mice before marked motor deficits occur, and indicate that behavioural training may act to suppress age-related gene expression alterations.

Poster Ref: P3-F-020

Theme: F: Nervous System Disorders

The amyloid cascade in iPSC-derived human neurons.

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Background: Our understanding of the molecular processes underlying Alzheimer's disease is still limited, hindering the development of effective treatments and highlighting the need for human-specific models. Advances in identifying components of the amyloid cascade are progressing, including the roles of the proteins clusterin and Dkk1 in mediating β-amyloid toxicity. This project aims to investigate the series of events initiated by Aβ that result in the neuronal degeneration in AD. Mutations in CLU and APOE, major genetic AD risk factors, have been introduced into human induced pluripotent stem cells (iPSCs) by precise genome editing. This will allow us to explore the specific effects of these mutations on neuronal response to Aβ.

Methods: iPSCs from a neurotypical male with a APOE ε3/ε3 genotype were differentiated into cortical neurons and treated with Aβ25-35 peptides. CRISPR cas9-mediated gene editing generated a CLU-knockout iPSC line and a knockin APOE line with ε4 genotype. The downstream effect of the Aβ exposure on the cells was measured by a high-throughput cytometry assay, optimised to identify changes in neuronal processes. Western blotting and qPCR assessed changes in protein and gene expression downstream of Aβ.

Results: The cell-imaging assay indicated that neuronal processes of the cells degenerate with increasing Aβ concentrations. We also observe that intracellular levels of clusterin are increased in cells treated with Aβ peptides. We are currently testing the neuronal differentiation of the CLU knockout cells in order to start testing for a phenotype and we are screening APOE knockin cells with the ε4 mutation.

Conclusions: We are establishing an isogenic model of sporadic AD with iPSCs of different genotypes, and determining the role of these major AD risk mutations in processing β-amyloid. Evaluating compounds that inhibit this pathway and assessing their effects on phosphorylated tau and cell toxicity in the neuronal cultures will be a key application of this modelling system.

Poster Ref: P3-F-021

Theme: F: Nervous System Disorders

Is small vessel disease a disease of the blood brain barrier?.

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Cerebral small vessel disease (SVD) is a vascular neurodegenerative disease which is the leading cause of vascular dementia and the cause of 20% of strokes. Its prevalence in the general population is also high, with 20-30% of those over 80 showing signs of the disease as white matter hyperintensities (WMH) on MRI scans. WMH treble the risk of stroke and double the risk of dementia. SVD is commonly thought to be caused by hypertension but 30% of sufferers are normotensive. A recently observed factor associated with sporadic SVD is loss of integrity of the blood brain barrier (BBB), which is also an ageing-related phenomenon, although the precise pathogenic role of the BBB in sporadic SVD is uncertain. To investigate this further, we studied brains from normotensive people with early stage SVD histopathologically and found that, compared to control brains, they had reduced capillary endothelial claudin-5 (a tight junction protein of the BBB; 6% ± 0.1% less; mean ± SEM), more oligodendrocyte precursor cells (OPCs; the precursors to myelinating oligodendrocytes; 190% ± 20% more), and more microglia/macrophages (175% ± 32% more). To further study the development of SVD we examined a relevant rat model of spontaneous SVD, the Stroke Prone Spontaneously Hypertensive Rat (SHRSP) and found that reduced endothelial claudin-5 was the earliest change (3% ± 0.01% less at 3 weeks), followed by OPC proliferation (186% ± 25% more at 4 weeks) and then increased number of microglia/macrophages (73% ± 7% more at 5 weeks). Importantly, all these changes occurred at a young age (< 5 weeks), before any measurable rise in blood pressure. Using an *ex vivo* slice culture model (*i.e.* removing blood flow) incubated over the same young ages we found these same changes occurred. This rules out direct damage by leakage of blood components through an impaired BBB, suggesting that an inherent endothelial cell dysfunction is the primary cause, with secondary BBB defects. This is supported by the observation of an increase in endothelial cell proliferation (44% ± 5% higher) in the SHRSP model. Further to this, preliminary data show a reduction in tight junctions between *in vitro* cultures of isolated endothelial cells from SHRSP compared to age matched controls.

Poster Ref: P3-F-022

Theme: F: Nervous System Disorders

Activation of the trace amine-associated receptor 1 reduces the motivation to seek methamphetamine and prevents drug-primed reinstatement of methamphetamine seeking.

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Strong evidence has emerged recently suggesting a prominent role of the trace amine-associated receptor 1 (TAAR1) in the functional regulation of dopamine transmission and psychomotor stimulant action. Several selective TAAR1 agonists have shown therapeutic-like potential in various animal models of cocaine addiction. However, the effects of pharmacological activation of TAAR1 on methamphetamine (METH)-induced behaviours are less known. Our previous observations showed a complex time-dependent interaction between METH and the partial TAAR1 agonist, RO5203648 (Cotter *et al.*, 2015). Here, we used the partial agonist, RO5263397, to further explore the modulatory effects of TAAR1 on METH reinforcement and relapse to METH seeking in rats. In experiment 1, we tested the ability of RO5263397 (0, 3, 10 mg/kg i.p.) to alter the break point for METH and food self-administration under a progressive ratio schedule of reinforcement. Partial TAAR1 activation reduced the break point for METH self-administration (0.05 mg/kg/infusion), but increased it when rats responded for food. In experiment 2, we evaluated the abuse liability of RO5263397 (0.25, 0.5 mg/kg/infusion) by making it available as a self-administered substitute for METH. Unlike a low dose of METH (0.017 mg/kg/infusion), which sustained strong responding when substituting for the training dose of METH (0.05 mg/kg/infusion), RO5263397 was not self-administered at any dose, thus exhibiting low abuse potential. In experiment 3, RO5263397 produced a strong but transient blockade of METH primed-induced reinstatement of METH seeking (during the first 2 hours, but not during the last hour, of the relapse test). Taking together, our data suggest that TAAR1 critically modulates clinically-relevant effects of METH and provides further support for using TAAR1 as a pharmacological target to develop anti-addiction medications.

Poster Ref: P3-F-023

Theme: F: Nervous System Disorders

The NMDA receptor antagonist memantine improves attention control in a carbon dioxide experimental human model of anxiety.

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Introduction: Inhalation of 7.5% carbon dioxide (CO_2) for 20 minutes increases subjective and physiological symptoms of anxiety and induces neuropsychological biases that characterise the anxiety phenotype. Some anxiolytics (*e.g.* lorazepam and paroxetine) can attenuate the subjective response to 7.5% CO_2 and suggest 7.5% challenge as a useful, translational model for treatment evaluation.

The moderate-affinity NMDA receptor antagonist memantine is clinically used in Alzheimer's disease and has positive effects across cognitive and behavioural symptoms. Pre-clinical studies suggest memantine may also have therapeutic potential in other conditions, for example, memantine has an anxiolytic effect in animal paradigms. However the anxiolytic effect of memantine in humans is unclear. We tested whether memantine can reduce anxiety and neuropsychological deficits during CO_2 challenge.

Method: 36 healthy volunteers were randomised to receive either a 2-week course of memantine (5mg titrated to 10mg on day 7) or placebo (balanced for gender, double-blind). On day 14 participants completed an eye-tracking attention task in which they had to control attention toward (prosaccade) or away (antisaccade) from negative and neutral images during inhalation of 7.5% CO_2 and air. Anxiety (questionnaire) and autonomic arousal (blood pressure and heart rate) were assessed at baseline and after each inhalation.

Results: 7.5% CO_2 significantly increased anxiety, heart rate and blood pressure, irrespective of drug group. Participants made significantly more antisaccade errors during CO_2 *vs.* air, consistent with our previous findings. Notably, the memantine group made significantly fewer antisaccade errors compared to placebo, particularly during CO_2-inhalation.

Discussion: Findings suggest that prior administration of memantine reduces the maladaptive effects of CO_2 on attention control. This positive effect occurred in the absence of changes in anxiety and autonomic arousal. Future research should test whether memantine can target deficits in attention control that characterize clinical anxiety disorders, and perseverative patterns of negative thinking (*e.g.* rumination and worry).

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Poster Ref: P3-F-024

Theme: F: Nervous System Disorders

Computational modelling of neural mechanisms of the emotional stroop effect in depression.

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Depression has been reported as robustly associated with increased response times at the incongruent, neutral, and negative-word trials of the classical and emotional Stroop tasks [1-3]. Response times for the negative-word trials in the emotional Stroop task have been reported to correlate with depressive severity, indicating strong relevance of the effect to the depressive symptomatology [3]. The current study proposes a novel integrative computational model of neural mechanisms of both the classical and the emotional Stroop effects, drawing on the previous prominent theoretical explanations of the classical Stroop effect [4-5], and in addition hypothesizing that negative emotional words function as conditioned stimuli for future negative outcomes. The model is shown to explain both fast and slow emotional Stroop effects, providing an advantage over the previous theoretical accounts [6-7]. Explorations for depressive abnormalities in the constructed model have revealed a candidate mechanism responsible for the pattern of depressive performance at the classical and the emotional Stroop tasks [3]. Results suggest that hyperactivity of the amygdala, together with increased inhibitory influence of the amygdala over dopaminergic neurotransmission, could be a plausible mechanism of the performance deficits at the tasks. Overall, the study presents a novel integrative framework of the mechanisms of classical and emotional Stroop effects, and proposes a plausible neural mechanism of increased response times at the tasks in depression.

[1] Holmes A. J., Pizzagalli D. A. (2008). Neuropsychologia, 46, 2904-2913.
[2] Mitterschiffthaler M. T., Williams S. C., Walsh N. D., Cleare A. J., Donaldson C., Scott J., Fu C. H. (2008). Psychological Medicine, 38, 247-256.
[3] Epp A., Dobson K., Dozois D., Frewen P. (2012). Clinical Psychology Review, 32, 316-328.
[4] Cohen J. D., Dunbar K., McClelland J. (1990). Psychological Review, 97, 332-361.
[5] Herd S. A., Banich M. T., O'Reilly R. C. (2006). Journal of Cognitive Neuroscience, 18, 22-32.
[6] Matthews G., Harley T. (1996). Cognition & Emotion, 10, 561-600.
[7] Wyble B., Sharma D., Bowman H. (2008). Cognition & Emotion, 22, 1019-1051.

Poster Ref: P3-F-025

Theme: F: Nervous System Disorders

RNA changes in SMN-deficient experimental cell models of Spinal Muscular Atrophy.

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Background: Spinal Muscular Atrophy (SMA) is a fatal neurodegenerative disease affecting primarily lower motor neurons. It is the major cause of death during infancy with no effective treatment to date. SMA is associated with homozygous deletion or mutation of the Survival Motor Neuron 1 gene (SMN1), which encodes the ubiquitously expressed protein SMN. SMN plays a crucial role in pre-mRNA splicing and it is also involved in axonal trafficking of mRNA-binding proteins and their target mRNAs. How SMN deficiency leads to selective loss of motor neurons is still unclear.

Objectives: In this study we aim, firstly, to identify transcriptome perturbations in SMN-deficient motor neurons using next generation RNA-sequencing (RNA-seq). Secondly, we plan to investigate potential axonal transport defects of candidate mRNAs using live cell imaging.

Methods and Results: To analyse splicing defects we have developed methods to extract RNA suitable for RNA-seq from whole cell extracts and cytoplasmic fractions of SMA type I human fibroblasts and healthy controls as well as primary cortical and motor neurons in which SMN expression is ablated by adeno-associated serotype 9 (AAV9) mediated RNAi. To analyse the effect of SMN deficiency on axonal transport of mRNAs identified through RNA-seq we have established an mRNA visualization system suitable for live imaging in primary neurons based on a bidirectional lentiviral vector.

Poster Ref: P3-F-026

Theme: F: Nervous System Disorders

Withdrawn

Poster Ref: P3-F-027

Theme: F: Nervous System Disorders

Experimental modelling of ALS by *in vitro* and *in vivo* modulation C9ORF72 gene.

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University of Sheffield

Background & objectives: So far, the repeat GGGGCC expansions located in the intronic region of the C9ORF72 gene is the most common mutation linked to Amyotrophic Lateral Sclerosis (ALS), being present in 40% of familial ALS and 8-10% of sporadic ALS cases. Since the discovery of the relationship between C9ORF72 and ALS, many studies have been focused on understanding the role of this protein and modelling the disease.

Here, we attempt to analyse the role of C9ORF72 in both, normal function and in ALS. To assess the normal function of C9ORF72 we knockdown this gene *in vitro* and *in vivo*. The effects of C9ORF72 repeat expansions were also investigated with the aim of potential gene therapy development.

Methods: miRNA sequences to knockdown C9ORF72 were designed to target the mouse gene and were cloned into lentiviral (LV) and adeno-associated viral (AAV) vectors. Cell lines and primary neurons were transduced and RT-PCR and WB experiments were carried out to test the mRNA and protein levels. *In vivo* experiments were also performed by injecting miRNA viral vectors in P1 mice. IHC and RT-PCR analysis were used to test the efficiency of the knockdown *in vivo*. To assess the effect of the expansions, LV and AAV vectors with GGGGCC repeat sequences from 10 to 102 were generated. Transduction assays using cell lines and primary neurons were performed to analyse the effects of the expansions, as well as the C9ORF72 RNA foci development by using *in situ* experiments. Neonatal mice were also infused with C9ORF72 expansions viral vectors and the effects associated with the expansions analysed.

Results: Viruses generated to silence C9ORF72 showed significant knockdown following cell transduction compared to scrambled control *in vitro*. C9ORF72 levels were also reduced *in vivo* and neuronal cells were efficiently transduced in brain and spinal cord. RNA foci development following transduction with viral-mediated repeat expansions has been observed in neurons *in vitro*. Histological data from animals injected with AAV9 expressing GGGGCC are being analysed. Our current studies will allow many avenues to open up in terms of C9ORF72 research into the function and potential treatments for C9ORF72-linked ALS.

Poster Ref: P3-F-028

Theme: F: Nervous System Disorders

HDAC6 inhibition as a therapeutic approach in Hereditary Spastic Paraplegia

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Sheffield Institute for Translational Neuroscience, University of Sheffield

Hereditary spastic paraplegias (HSPs) are a heterogeneous group of inherited neurological disorders that are characterised by lower limb spasticity and weakness. The clinical pathophysiology is degeneration of axons in the corticospinal tract. The most common gene, which is responsible for 40% of HSP, is spastin (Spast). Spast encodes a microtubule-binding protein that has several important roles in the cell including vesicle trafficking and microtubule severing. Mutations in Spast cause reductions in axonal transport that lead to mitochondrial accumulation in axonal swellings in the corticospinal tract. Mice carrying a human pathogenic mutation develop a progressive gait defect. Microtubule acetylation has been shown to regulate axonal transport; increased acetylation correlates with upregulation of axonal transport. One way to increase microtubule acetylation is to inhibit the key enzyme responsible for reducing microtubule acetylation, histone deacetylase 6 (HDAC6). Inhibition of HDAC6 to restore axonal transport has been shown to be neuroprotective in several models of neurodegenerative disease.

The aim of this project is to test the hypothesis that increasing microtubule acetylation *via* chemical or genetic inhibition of HDAC6 will restore axonal transport and correct the gait defect in the mouse model of HSP. (i) To generate cohorts of Spast+/+ and SpastΔE7/ΔE7 (null mutant) mice for *in vivo* studies with pharmacological HDAC6 inhibition, (ii) To breed a cohort of double mutant mice that are HDAC6 null and SpastΔE7/ΔE7 to test the effect of genetic silencing of HDAC6, and (iii) To test the effects of HDAC6 inhibition on axonal transport in primary neurons.

Crosses have been set up to generate double mutant mice that are HDAC6 null and SpastΔE7/ΔE7. HDAC6 inhibitor compounds have been used for a pilot dosing experiment and showed increased tubulin acetylation in CNS and peripheral tissues. Cohorts of Spast+/+ and SpastΔE7/ΔE7 mice have been generated and gait is being studied every month using a Catwalk apparatus. At 9 months of age the mice were randomly assigned to treatment and control groups, to be treated with a CNS penetrant HDAC6 inhibitor. We will determine the effect of treatment on the HSP-related gait defect.

Poster Ref: P3-F-029

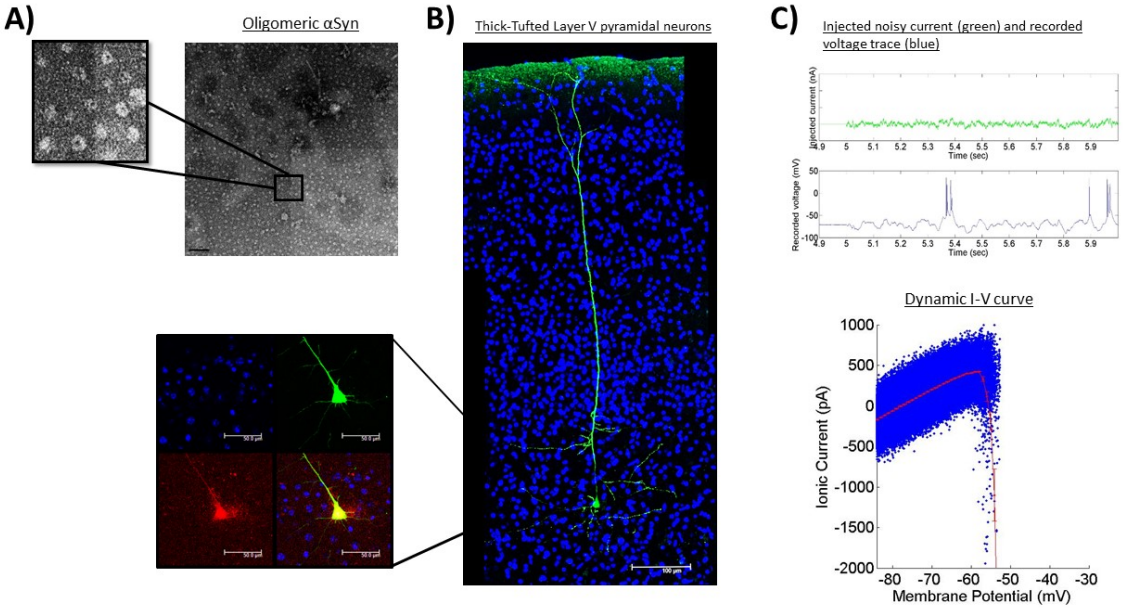
Theme: F: Nervous System Disorders

Impact of soluble oligomeric alpha-Synuclein on the electrophysiology of neocortical neurons in mice.

Timothy J Kaufmann, Paul Harrison, Magnus JE Richardson, Teresa JT Pinheiro and Mark J Wall

School of Life Sciences, University of Warwick

Alpha-Synuclein (αSyn), a presynaptic protein found abundantly throughout the brain, was one of the first proteins to be pathologically associated with Parkinson's disease (PD). This association came initially from identifying αSyn as the main component of neuritic plaques found in disease patients. Indeed, the detection of αSyn-containing plaques has become a clinical hallmark across numerous neurodegenerative disorders collectively termed Synucleinopathies. Point mutations in αSyn as well as gene multiplications both result in early onset PD through changes in the molecular and biophysical properties of αSyn aggregation. Increasing evidence suggests that it is soluble oligomeric intermediates that are the main species responsible for neurotoxicity, disease propagation and cell death rather than the large insoluble aggregates. Both *in vitro* and *in vivo* studies have generated numerous theories on the mechanism of toxicity including: membrane permeabilisation, Ca^{2+} influx, synaptic alterations and mitochondrial dysfunction. Evidence for these pathologies are supported by recent investigations that have shown changes in hippocampal LTP and effects on AMPA-receptor-mediated synaptic transmission in the presence of extracellularly applied αSyn oligomers. However, the in-depth electrophysiological analysis needed to link these proposed mechanisms to observed neuronal changes is still lacking. The aim of our work is to quantify changes in the specific response properties of thick-tufted layer 5 (TTL5) pyramidal neurons following the injection of different structurally defined αSyn oligomeric constructs. Electrophysiological parameters were extracted from TTL5 neurons using the dynamic I-V curve method (Badel *et al.*), with the accuracy of the derived parameters tested using an exponential-integrate and fire model. Changes in cell capacitance, time constant and action potential amplitude are consistent with oligomers accumulating within the cell and interfering with current spread.



Structurally characterised αSyn oligomers (A) are applied intracellularly to TTL5 pyramidal neurons in the neocortex of mice by whole-cell patch clamping (B). The injected noisy current and recorded voltage (C top) generate a dynamic I-V curve (C bottom) from which electrophysiological parameters are extracted. (EM = 100nm; Confocal = 100μm, inset = 50μm, green=Af488 dye, red=αSyn, blue=DAPI)

Poster Ref: P3-F-030

Theme: F: Nervous System Disorders

Characteristics of evolving epileptiform activity in brain slices.

Neela Krushna Codadu and Andrew Trevelyan

Newcastle University

Organised and structured neuronal activities are qualities of normal brain function. However, then there is a tendency for the network to become hyperexcitable if the network tips over some apparent threshold level of excitation, or below some threshold level of inhibition, although this process, termed ictogenesis is not understood. This hyperexcitable state of the network underlies the pathological condition of seizures. It is important therefore to distinguish between different pathological mechanisms that contribute to the hyperexcitable state.

Epileptiform activity can be readily induced in brain slices prepared from wild-type mice by bathing in different pro-epileptic bathing media, including $0Mg^{2+}$, and 4-aminopyridine (4-AP). However, the distinctive patterns of activity do not develop instantly, but rather evolve over a period of many minutes to hours. We therefore developed a set of measurements to characterise the evolution of epileptiform activity. Post hoc analysis of these different measures has been performed.

We made extracellular field recordings from multiple locations in neocortex, in horizontal slices prepared from young adult mice. We analysed the times ictal events, the pattern of inter-ictal activity, and the transition to a late pattern that has been likened to status epilepticus (Heinemann *et al.*, 1994). We also measured changes in the speed of the ictal wavefront propagation, which is determined by efficacy of feedforward inhibition ahead of the ictal wavefront (Trevelyan *et al.* 2007). We found marked differences in the patterns of evolution of these various patterns of activity.

In both $0Mg^{2+}$ and 4AP models, the first full ictal event occurred after a relatively long time, 670.1±71s and 910.91±99s, respectively. There was a small subsequent increase in the rate of ictal events in the $0Mg^{2+}$ model, but in the 4AP model, subsequent events occurred at a steady rate. The speed of the wavefront showed a more gradual progressive increase with each successive event. In contrast, the rate of occurrence of interictal events was remarkably stable, at 0.14±0.02Hz, suggesting that this rate is set by factors that, unlike synaptic properties, are invariant. We speculate that glial behaviour may underlie these events.

Poster Ref: P3-F-031

Theme: F: Nervous System Disorders

Failure of hippocampal deactivation with loss events in treatment-resistant depression.

Blair Johnston[1], Serenella Tolomeo[1], Victoria Gradin[2], Mairi Stirling[1], Karen Walker[3], David Christmas[3], Jennifer Macfarlane[3], Keith Matthews[1] and Douglas Steele[1]

[1]University of Dundee, [2]Universidad de la Republica, Uruguay, [3]NHS Tayside

Whilst anhedonia is often investigated in depression, responses to aversive events are less often investigated. Deakin and Graeff proposed that, in depressed patients experiencing aversive stimuli, prolonged rumination could be caused by the failure or underactivity of the median raphe nucleus (MRN) leading to hippocampal overactivity (Deakin, "The origins of '5-HT and mechanisms of defence' by Deakin and Graeff: A personal perspective", 2013, J. Psychopharmacol). The authors proposed that the MRN resilience system normally functions to interrupt rehearsal of ruminative aversive memories and when it fails or is underactive, prolonged rumination results in the elaboration of such memories. Quantitative methods such as machine learning combined with feature selection on neuroimaging data have the potential to identify objective biomarkers for depression that help to elucidate the causes of depression and diagnose individual patients. Brain regions identified using these techniques could reveal a consistent underlying abnormality in patients.

Here we describe predictions of treatment-resistant depression (TRD) diagnosis using within study replication and an instrumental reward and loss fMRI paradigm obtained from nineteen adults with TRD and nineteen never-depressed controls. Regions identified as relevant to predicting diagnosis were identified through feature selection.

We report 84% and 97% accuracy of individual subject diagnostic prediction using reward and loss responses respectively. Reduced activity in the nucleus accumbens and medial orbitofrontal cortex during rewarding events and increased activity in the hippocampus during loss events were identified as most supporting TRD diagnosis (see attached Figure). The brain regions that showed abnormal activity in the loss images were also found to be correlated with various severity scores.

The identification of hippocampal overactivity in response to aversive events, and a correlation between failure of hippocampal deactivation with loss events and increased BHS hopelessness, support Deaken and Graeff's hypothesis. Response to aversive stimuli is an under-studied and important research area that may provide a biomarker of depression and increase understanding of TRD.

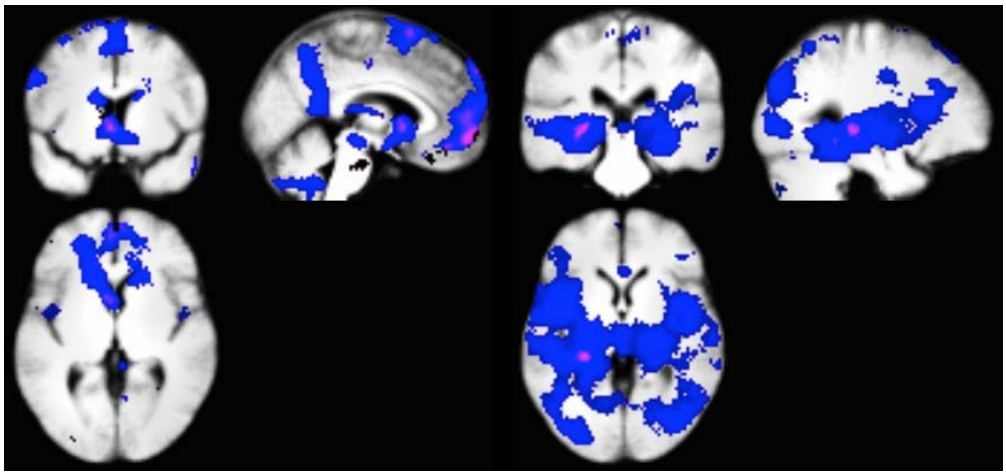


Figure Legend: The overlap between the regions identified during group-level analysis (blue and pink) and the brain regions identified during the classification of TRD patients and controls (pink) using the win contrast (left) and the lose contrast (right).

Poster Ref: P3-F-032

Theme: F: Nervous System Disorders

Defining the nature and progression of spinal cord and brainstem pathology in Ppt1-/- mice.

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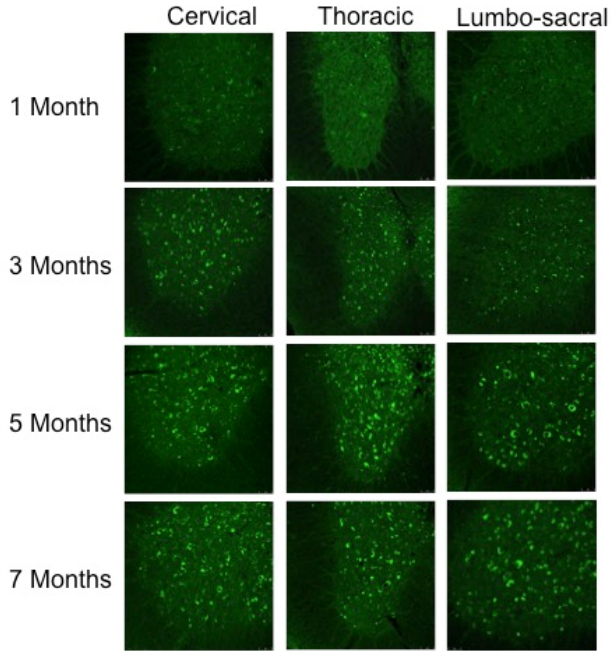
The neuronal ceroid lipofuscinoses (NCLs) are a group of up to fourteen autosomal recessively inherited, monogenetic, progressive, neurodegenerative lysosomal storage disorders, which affect children and young adults. These mutations occur in either soluble lysosomal enzymes or transmembrane proteins within the lysosomal system, in cells throughout the body. Infantile NCL (INCL) is caused by the deficiency of the lysosomal enzyme palmitoyl protein thioesterase-1 (PPT1) and is the most rapidly progressing form of NCL. Like all other forms of NCL, there is currently no effective therapy for INCL. The characterization of Ppt1 null mutant mice (Ppt1-/-) has provided a wealth of data about the relationship between glial activation and neuron loss within the forebrain. Although forebrain directed AAV-mediated gene therapy significantly prolongs life span, these mice nevertheless still die prematurely. These data prompted us to investigate whether other regions of the central nervous system that were not therapeutically targeted may also contain significant neuropathology. We focused our analysis upon the brainstem and spinal cord, which have not been characterized in any detail in any form of NCL. Our findings reveal that there is indeed an extensive and progressive neurodegenerative process that occurs in the brain stem and spinal cord, which is evidenced by profound glial activation and neuron loss. This appears to affect both motor and sensory pathways, and displays a rostro-caudal gradient. These neuropathological changes worsen with time, but are untouched by therapeutic approaches that target the forebrain. These data not only define the extent and nature of brain stem and spinal cord pathology, but also reveal these brain regions as important targets for future therapeutic approaches.



Confocal microscopy images taken at 1,3,5 and 7 months of the cervical, thoracic and lumbo-sacral spinal cord of mutant Ppt1-/- mice, showing the pathognomic accumulation of autofluorescent storage material in the grey matter over time.

Poster Ref: P3-F-033

Theme: F: Nervous System Disorders

Early gene expression changes induced by intense cortical activation.

Robert Parrish, Neela Codadv, Claudia Racca and Andrew Trevelyan

Newcastle University

The genes and proteins expressed by a neuron determine its excitability, and *vice versa*, its activity also influences these expression patterns. This two-way interaction maintains functional stability and regulates metabolic requirements, both key homeostatic mechanisms. On the other hand, non-homeostatic changes occur during development and learning. Similarly, various brain insults can trigger non-homeostatic changes, leading to a long-lasting change in excitability, manifest as a tendency to suffer epileptic seizures. This process is termed epileptogenesis. It is a complex and poorly understood cascade of cellular and network changes, for which there is no prophylactic clinical therapy. The balance between homeostatic and non-homeostatic changes is likely to provide important clues as to how epilepsy develops.

Epileptogenesis can be triggered *in vivo* by periods of status epilepticus. It is not known though what roles are played by the different elements within the network, namely the pyramidal cells, glia and the different classes of interneurons. We set out to explore this utilizing several different *in vitro* models of epileptiform event. We will present evidence from patch clamp and Ca^{2+} network imaging to illustrate how these can be used to generate stable patterns of activity involving very different subsets of the cortical network. We have described already the pattern of full neuronal participation induced by bathing brain slices in $0Mg^{2+}$ ACSF (Trevelyan *et al.*, 2006, 2007). We show here using a novel immunohistochemical analysis, that interictal events and preictal events show disproportionate activity in the interneuronal population. We also show a means of inducing an almost purely interneuronal activation using 4-aminopyridine with glutamatergic blockade.

We next show how we can use these *in vitro* models to separate out the homeostatic responses of different neuronal elements within the network. We present RT-PCR analysis showing how epileptiform activity over the course of an hour, can induce acute changes in the expression of several regulatory genes including mTOR, BDNF, REST and PGC1a. We further show intriguing differences in the pattern of gene regulation in the different cortical subfields.

Poster Ref: P3-F-034

Theme: F: Nervous System Disorders

Methionine increases BDNF DNA methylation and improves memory in epilepsy.

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[1]Newcastle University, [2]University of Alabama at Birmingham, USA

Objective: Temporal lobe epilepsy (TLE) patients exhibit signs of memory impairments even when seizures are pharmacologically controlled. Surprisingly, the underlying molecular mechanisms involved in TLE-associated memory impairments remain elusive. Memory consolidation requires epigenetic transcriptional regulation of genes in the hippocampus; therefore, we aimed to determine how epigenetic DNA methylation mechanisms affect learning-induced transcription of memory-permissive genes in the epileptic hippocampus.

Methods: Using the kainate rodent model of TLE and focusing on the brain-derived neurotrophic factor (Bdnf) gene as a candidate of DNA methylation-mediated transcription, we analyzed DNA methylation levels in epileptic rats following learning. After detection of aberrant DNA methylation at the Bdnf gene, we investigated functional effects of altered DNA methylation on hippocampus-dependent memory formation in our TLE rodent model.

Results: We found that behaviourally driven Bdnf DNA methylation was associated with hippocampus-dependent memory deficits. Bisulfite sequencing revealed that decreased Bdnf DNA methylation levels strongly correlated with abnormally high levels of Bdnf mRNA in the epileptic hippocampus during memory consolidation. Methyl supplementation *via* methionine (Met) increased Bdnf DNA methylation and reduced Bdnf mRNA levels in the epileptic hippocampus during memory consolidation. Met administration reduced interictal spike activity, increased theta rhythm power, and reversed memory deficits in epileptic animals. The rescue effect of Met treatment on learning-induced Bdnf DNA methylation, Bdnf gene expression, and hippocampus-dependent memory, were attenuated by DNA methyltransferase blockade.

Interpretation: Our findings suggest that manipulation of DNA methylation in the epileptic hippocampus should be considered as a viable treatment option to ameliorate memory impairments associated with TLE.

Poster Ref: P3-F-035

Theme: F: Nervous System Disorders

The clinically-effective smoking cessation agent varenicline restores cognitive deficits associated with nicotine withdrawal in a probabilistic reversal task in rats.

Anne Jackson[1], Yazead Buhidma[2], Sarah Silk[2] and Mohammed Shoaib[2]

[1]Brighton University, [2]Newcastle University

There is recognition that cognitive problems can contribute to renewed drug taking in former addicts. Our previous work has indicated that current smokers show reduced performance on a probabilistic reversal learning (PRL) task, relative to former smokers (Butler *et al.*, 2011). To establish if this cognitive impairment was due to nicotine in tobacco, a nicotine withdrawal model was developed in rodents trained to perform a PRL task. Another goal of this study was to examine varenicline, an alpha4beta2 partial agonist for its ability to restore the cognitive impairment. Male hooded rats that exhibited stable levels of performance in the PRL task were made dependent on nicotine *via* osmotic minipumps implanted for 7 days (3.16mg/kg/day). Repeated tests in the PRL task at specified withdrawal time points revealed peak cognitive disruption at 12 and 24 hours following surgical removal of the minipumps (n=8). In a subsequent experiment, nicotine (0.2 mg/kg SC, varenicline (0.3 & 1.0 mg/kg SC) or vehicle administered 10 min prior to PRL test sessions at 12 and 24 hours from pump removal demonstrated a significant amelioration of performance deficits. Relative to pre-withdrawal baselines, animals in the vehicle group showed significant deficits in the number of reversals ($p<0.01$), speed of responding ($p<0.02$) and increases in omissions ($p<0.01$) peaking at 24 hrs withdrawal. Comparisons between drug treatment groups with vehicle, at 24 hrs withdrawal, revealed significant reduction in reversal deficits by all drug treatments ($p<0.01$). Slower speed of responding was significantly ameliorated by nicotine ($p<0.02$) and by varenicline 1 mg/kg ($p<0.01$). The high dose of varenicline only, reduced omissions ($p<0.05$). These results confirm the role of nicotine to induce dependence and its withdrawal to disrupt PRL performance. Furthermore, demonstration that current smoking cessation treatments can restore withdrawal-induced disrupted cognitive performance provides a valuable model to develop putative new treatments for smoking cessation.

Butler K, Rusted J, Gard P, Jackson A (2011) Probabilistic Reversal Learning Behaviour in Current, Former and Never Smokers. 13th Annual European Meeting of the Society for Research on Nicotine and Tobacco (SRNT-E) Turkey.

Poster Ref: P3-F-036

Theme: F: Nervous System Disorders

Neuroprotective effects of nicotinamide against Aβ(1-42) induced *in vivo* and *in vitro* neurodegeneration models.

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Introduction: Alzheimer's Disease (AD) is the most common form of dementia and characterized by senile plaques and neurofibrillary tangles. The underlying mechanisms of AD are not clarified yet but oxidative stress and mitochondrial dysfunction are important features of its neuropathogenesis. The aim of the present study was to investigate the protective effects of nicotinamide (NA) against amyloid β-peptide 1-42 induced *in vivo* and *in vitro* neurodegeneration models.

Methods: Sprague-Dawley rats were divided into seven groups as control-1, control-2 Aβ(1-42), Aβ(1-42)+NA (100 mg/kg and 500 mg/kg) and NA (100 and 500 mg/kg). For *in vivo* neurodegeneration; control-1 and Aβ(1-42) groups were stereotaxically injected bilaterally into the hippocampus with either 1 µl of saline or 1 µl of aggregated Aβ(1–42) (5 µg/µl). After surgery NA injections were made intraperitoneally for seven days. For *in vitro* neurodegeneration; rats were injected intraperitoneally with NA (100-500 mg/kg) or with saline for seven days. Synaptosomes isolated from control-2 and NA groups were incubated with 10 µM and 30 µM Aβ(1-42) or saline for 6 h at 37˚C. To investigate the effects of Aβ(1-42) and NA; protein carbonyls (PCOs), lipid peroxidation (TBARS), reactive oxygen species (ROS) production (DCF) and mitochondrial function (MTT) were measured in hippocampal tissues and synaptosomes using spectrophotometric and spectrofluorimetric methods.

Results: While Aβ(1-42) treatment increased the oxidative stress parameters (PCOs, TBARS, DCF) and decreased mitochondrial reduction capacity, NA treatments against Aβ(1-42) were found significantly to improve mitochondrial function and decreased the oxidative stress parameters in experimental *in vivo* neurodegeneration. In addition, synaptosomes isolated from NA injected rats then treated *in vitro* with Aβ(1-42) showed significant decreases in lipid peroxidation, ROS production and protein oxidation when compared to Aβ(1-42) incubated control synaptosomes. NA was also found to elevate the mitochondrial reduction capacity against Aβ(1-42) in synaptosomes.

Discussion: Nicotinamide may be helpful as a therapeutic agent in neurodegenerative processes due to the decreased levels of oxidative stress and improvement of mitochondrial function.

Poster Ref: P3-F-037

Theme: F: Nervous System Disorders

Development of a cell-penetrating peptide for the delivery of antisense oligonucleotides to spinal muscular atrophy mice.

Melissa Bowerman[1], Corinne A Betts[1], Frank Abendroth[2], Gareth Hazell[1], Graham McClorey[1], Francesco Catapano[3], Haiyan Zhou[3], Francesco Muntoni[3], Michael J Gait[2], Matthew JA Wood[1] and Suzan M Hammond[1]

[1]Department of Physiology, Anatomy and Genetics, University of Oxford, [2]Medical Research Council, Laboratory of Molecular Biology, Cambridge, [3]Dubowitz Neuromuscular Centre, Institute of Child Health, University College London

SMA results from loss of the survival motor neuron 1 (SMN1) gene and is characterized by loss of motoneurons and muscular atrophy. Most eukaryotes have a single copy of SMN1. In humans however, a genomic duplication gave rise to a second gene, SMN2. The 2 genes are 99% identical except for 5 nucleotides. Of these, a critical difference lies at position 6 of exon 7, where a C to T substitution in SMN2 leads to aberrant splicing of exon 7 and production of an unstable SMNΔ7 protein. Thus, SMN1 expresses the full-length (FL) SMN protein while SMN2 mostly produces the SMNΔ7 protein, although always generating a small amount of FL protein. Whilst loss of SMN1 causes SMA, SMN2 modulates disease severity through copy number: as the number of SMN2 copies increases, so does the FL protein. Therapeutic interventions have thus focused on promoting SMN2 exon 7 inclusion. Recently, the use of antisense oligonucleotides (ASOs) that bind SMN2 mRNA, modify its splicing and induce exon 7 inclusion, has emerged as a viable therapy for SMA. ASOs show promise in SMA mice and are being evaluated in a phase I clinical trial. However, they require invasive administration methods for adequate delivery to the CNS. An alternate method is to covalently conjugate the ASO to a cell-penetrating peptide (CPP). We have developed such a peptide-conjugated ASO (Pip6a) that efficiently modulates splicing in various tissues of DMD mice when delivered *via* a less invasive intravenous injection. Further, we have evaluated Pip6a-ASO in neonatal SMA mice and observe a significant upregulation of FL SMN2 in CNS and peripheral tissues, rescue in lifespan and overall improvement of neuromuscular phenotype. Pip6a-ASO also crosses the blood brain barrier in adult mice, albeit at a higher dose. Seeing as only a small fraction of possible CPP designs has been explored, our objective is to generate a novel CPP that can more effectively penetrate CNS and peripheral tissues in adult mice and display an enhanced favorable toxicity profile. Here, we present the CPPs evaluated so far, which are conjugated to a previously validated ASO and evaluated in WT mice that express human SMN2. The goal of this project is to develop a novel clinically amenable and relevant CPP-ASO approach for SMA.

Poster Ref: P3-F-038

Theme: F: Nervous System Disorders

Contribution of striatal astrocytes to intrastriatal processes subserving cocaine seeking habits.

Maxime Fouyssac[1], Mickaël Puaud[1], Guylène Page[2], Barry Everitt[3], Thierry Janet[2] and David Belin[1]

[1]Department of Pharmacology, University of Cambridge, [2]CIMOTHEMA EA3808, University of Poitiers, France, [3]Department of Psychology, University of Cambridge

Cocaine addiction has been suggested to result from loss of control over maladaptive drug seeking habits. The transition from volitional drug use to compulsive drug seeking habits is subserved by a shift in the locus of control over behaviour from the nucleus accumbens to the dorsolateral striatum.

The spread of neurobiological adaptations from the ventral to the dorsolateral striatum over the course of cocaine exposure has been associated with alterations of the expression of the dopamine transporter (DAT), the target of cocaine. Whereas these alterations have been considered to be related to neuronal mechanisms, the DAT is also expressed in astrocytes which have been involved in the pathophysiology of drug addiction. We have therefore investigated whether decreases in DAT protein levels following cocaine exposure could be attributable to adaptations in astrocytes.

For this, rats were exposed either to short term cocaine self-administration under continuous reinforcement or to three weeks of training under a second order schedule of reinforcement. Whereas the former training procedure has been shown to goal-directedness over behaviour, the latter promotes dorsolateral striatum-dependent drug seeking habits. We compared these two cocaine experienced groups both to a control, naive group and rats which have been trained to lever press for food. Following training, brains were harvested and samples of various striatum territories (nucleus accumbens core, dorsomedial and dorsolateral striatum) were processed either for western blotting (from micro punches of frozen brain sections) or primary astrocytes culture (from the same striatal areas from fresh brains). As compared to naive or food controls, cocaine exposed groups both shown a decrease in DAT levels in the striatal territories as observed from whole tissue extracts. This decrease may be attributable to the complete blunt of the expression of the protein in astrocytes quantified from cultures.

These data show that intrastriatal glial adaptations in DAT levels may predate the establishment of cocaine seeking habits, thereby suggesting a unique causal contribution of astrocytes in the intrastriatal processes ultimately leading to the devolvement of control over behaviour to the dorsolateral striatum.

Poster Ref: P3-F-039

Theme: F: Nervous System Disorders

The autism associated gene Cyfip1 is critical for the maintenance of dendritic complexity and synapse stability.

Elizabeth Davenport, Manavendra Pathania, Blanka Szulc, David Sheehan, Guillermo López-Doménech and Josef Kittler
University College London

Copy number variation (CNV) at the 15q11.2 region of the genome has been identified as a significant risk locus for neuropsychiatric disorders such autism spectrum disorder (ASD), schizophrenia (SCZ), intellectual disability and epilepsy. Of the genes present at this locus, Cyfip1 is particularly interesting because its expression is upregulated in post mortem brains from ASD patients with the 15q11.2 duplication. Furthermore, deletions in Cyfip1 have been identified in ASD and SCZ patients. Taken together, Cyfip1 is emerging as a candidate gene for neuropsychiatric disorders and therefore, understanding how CNV in Cyfip1 impairs neuronal and synaptic development is an important goal.

The formation of synapses and the correct development of neural networks depend on signalling pathways that control cytoskeletal structure. Indeed, several genes encoding major actin regulators have been associated with neurological disorders. The protein CYFIP1 and its homolog CYFIP2 are known key regulators of actin dynamics. They form a component of the WAVE regulatory complex, which initiates actin polymerisation following Rac1 activation. Determining the role of CYFIP proteins in neuronal and synapse development is of great importance for understanding their links to neuropsychiatric disorders.

Here we alter Cyfip1 dosage, by overexpression or mouse genetics, to investigate how CNV in Cyfip1 affects actin dynamics and impacts on dendritic and synaptic stability. We show CYFIP1 is highly enriched at synapses and its overexpression results in disrupted neuronal morphology and synapse stability. On the other hand, loss of CYFIP1 alters dendritic arborisation and F-actin assembly at synapses. Interestingly, both overexpression and loss of CYFIP1 impact on dendritic complexity and synapse stability. We conclude that altered levels of CYFIP1 lead to pathological changes in CNS maturation and neuronal connectivity that may contribute to the development of the neurological symptoms seen in ASD and SCZ.

Poster Ref: P3-F-040

Theme: F: Nervous System Disorders

Exogenous netrin-1 normalizes the delayed trans-synaptic enhancement in neurotransmitter release induced by distal axon injury.

Tharkika Nagendran, Rebecca Bigler, Rylan Larsen, Benjamin Philpot and Anne Taylor

UNC-Chapel Hill, Chapel Hill, NC, USA

Distal injury of long pyramidal tracts remodels cortical maps by enhancing excitability, yet the mechanisms underlying this plasticity are poorly understood. We found that distal axotomy of pyramidal neurons induced the loss of dendritic spines onto axotomized neurons, followed by a delayed trans-synaptic and transcription-dependent enhancement of neurotransmitter release. Axotomy significantly decreased expression of the secreted factor, netrin-1. Further, the application of exogenous netrin-1, which is found in the mature brain, normalized the axotomy-induced changes in neurotransmitter release. These findings suggest netrin-1 may be a therapeutically-relevant target within a tractable time-window for modulating excitability following brain injury.

Poster Ref: P3-F-041

Theme: F: Nervous System Disorders

Randomised double blind deep brain stimulation (DBS) of ventral anterior capsule/nucleus accumbens and/or subgenual cingulate in severe and chronic treatment refractory Major Depressive Disorder (MDD). Clinical and imaging results and five year follow up.

Andrea L Malizia[1], Peter Talbot [2], Shazia Jawed [1], Ann Rich[1], Claire Durant [1], Julian Matthews [2], Robin Holmes [1], Sue Wilson[1], Sonny Khan[1] and Nikunj K Patel[1]

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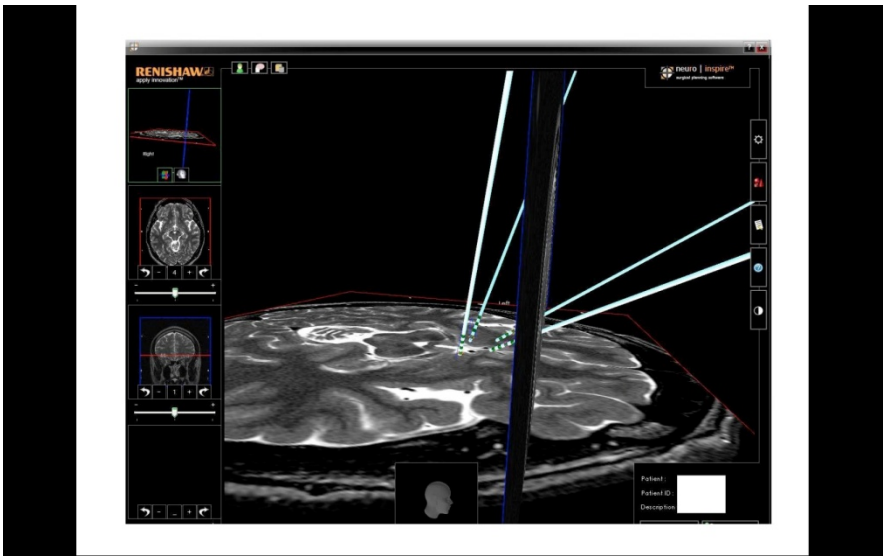
Eight patients with severe and enduring MDD were implanted with two DBS electrodes on each side of the brain- four in total. Two were placed with the tip in the nucleus accumbens 4 mm in front of the anterior commissure and with the fourth contact in the ventral anterior capsule. Two were placed in the white matter adjacent to the ventral anterior cingulate with the tip in its most posterior part and the fourth contact about 2/3 of the distance from the most posterior part of the ventral cingulate to the genu. Patients were randomised to start stimulation in either nucleus accumbens or posterior subgenual cingulate (in the same coordinates as Brodmann area 25 as defined in the Tailarach atlas). Stimulation parameters were adjusted at regular intervals and if there had been no response or if the patient decided that the response was not good enough, stimulation was started in an alternative location. If a patient did not respond to single stimulation in any of the locations, more than one location would be stimulated at once until all reasonable combinations had been tried. Remission was defined as a MADRS score <9 while response was defined as a 50% or more decrease in MADRS score. 3/8 patients remitted, 2/8 responded and 3/8 did not respond (one dropping out of the study). Stimulation in the nucleus accumbens or in the posterior subgenual cingulate did not produce any long lasting benefits. Stimulation in the ventral anterior capsule was the most efficacious although stimulation of the anterior part of the subgenual cingulate also resulted in improvement. Perfusion was increased in many parts of the frontal lobes and decreased in medial temporal structures when comparing remitters with non remitters or responders with non responders. The three remitters were stimulated only in one region while the two responders were stimulated in two regions simultaneously. Long term follow up revealed that all responders/remitters relapsed if DBS was accidentally switched off. Restarting DBS after such events resulted in repeated response but a change in stimulation parameters was needed. One patient who had remitted committed suicide after one such event. One patient who had not responded remitted with ablative neurosurgery while the other two are still severely unwell.



Planning MRI scan showing trajectory and position of DBS leads introduced through guide tubes at surgery.

Poster Ref: P3-F-042

Theme: F: Nervous System Disorders

ICCAM platform study: An fMRI investigation into the effects of neurokinin 1 antagonism on response to aversive images in abstinent alcohol and polydrug dependent individuals.

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Introduction: Treatments for addiction are limited and relapse following periods of abstinence constitutes a continuing challenge. Dysregulation of distinct neural networks are thought to underpin different relapse pathways, such as reward, impulsivity and stress-related networks. Understanding the neuropharmacology of these networks is likely to provide new targets for treatment.

Neural responses to stress/emotional salience can be probed by visual imagery fMRI tasks which engage amygdala responses. These have previously been used to demonstrate altered emotional responses in alcohol, cocaine and heroin dependence, and, in alcoholics, modulation by neurokinin 1 (NK1) antagonism.

We aimed to investigate the effect of NK1 antagonism on response to aversive stimuli using an Evocative Images task.

Method: Alcohol dependent (AD), polydrug dependent (PD, ≥2 substance dependencies excluding nicotine) and healthy control participants received an NK1 antagonist (vofopitant/aprepitant, 10mg/80mg, oral) or placebo in a double-blind design, 2 hours before fMRI scanning using an Evocative Images task. This task consists of images from the International Affective Pictures System (IAPS) library, comprising aversive or neutral images in a block design, balanced for valance and arousal. The contrast examined was the BOLD signal change between aversive and neutral images. Data were acquired from 20 AD, 32 PD and 33 controls. Whole brain voxelwise analyses were carried out using FSL (cluster corrected $Z > 2.3$, $p < 0.05$).

Results: The PD group showed increased BOLD response to aversive images relative to controls. In the PD group NK1 antagonism significantly reduced BOLD in the left insula and right frontal pole compared with placebo. A group by drug interaction showed NK1 antagonism significantly reduced BOLD response to aversive images in the left amygdala, left putamen and hippocampus bilaterally in the PD group relative to controls. These effects were not observed in the AD group.

Conclusion: NK1 antagonism differentially modulated the BOLD response to aversive images in PD, AD and control groups. The hyper-response to stressful images observed in PD participants was attenuated, suggesting potential for NK1 antagonists to reduce stress-induced relapse in abstinent polydrug addicts.

Poster Ref: P3-F-043
Theme: F: Nervous System Disorders

Deletion of GABAA receptor alpha4 subunits reduces alcohol consumption in a mouse model of binge drinking.

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GABAA receptors (GABAARs) mediate inhibitory neurotransmission throughout the CNS. GABAARs are heteromeric complexes that can be divided into several classes based on their subunit composition. GABAAR α4 subunits predominantly partner with δ subunits to form extrasynaptic receptors which mediate tonic inhibition of neurons.
The α4 subunit is expressed throughout the thalamus, hippocampus and striatum; particularly in the Nucleus Accumbens (NAc). Studies in rats have found that down-regulation of α4 in the NAc reduces alcohol consumption during chronic access conditions.

To further investigate the influence up or down-regulating α4-GABAAR function on voluntary alcohol consumption we used the “Drinking in the dark” procedure (DiD). DiD gives mice limited access to ethanol during a 2 hour period starting 3 hours after lights off (12 hour light/dark schedule) over 3 days. At this time C57BL/6J mice voluntarily drink high volumes of alcohol within a restricted time period. This makes DID a valid model of binge drinking relative to other procedures in which ethanol is provided chronically or administered by an experimenter.

To study the effects of increased α4 GABAAR activity in the NAc we used THIP (a GABAAR agonist that is selective for extrasynaptic GABAARs). Stereotaxic implantation of indwelling cannulae allowed us to administer 1ul bilateral infusions of either THIP (3mM) or saline directly to the NAc in C57BL/6J mice prior to the DID procedure. THIP was administered directly before a 2hr test period in which mice were given access to a 20% (v/v) ethanol solution. The THIP treatment led to a significant increase in alcohol consumption compared to saline-treated controls.

To study down-regulation of α4-GABAAR function we compared ethanol consumption (15% (v/v)) in DiD between mice with varying levels of α4 expression. Constitutive knock-out (gabra4 KO) mice were compared with WT and heterozygote (HET) littermates. KO mice drank significantly less than either WT or HET mice. We found no difference between WT and HET mice.

Previous studies have found that reduced expression of both α4 and δ GABAAR subunits decreases alcohol consumption during chronic access conditions. Our data suggest α4-GABAARs also play a role in mediating binge-like drinking.

Poster Ref: P3-F-044

Theme: F: Nervous System Disorders

Single unit action potentials in humans and the effect of seizure activity.

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Spike-sorting has been employed to assess firing patterns of isolated neurons (“single units”) from implanted electrode recordings in patients undergoing assessment for epilepsy surgery, but we do not know their potential for providing useful clinical information. It is important therefore to characterise both the stability and context of these recordings. A critical consideration is the location of these units with respect to the focus of the pathology. Recent analyses of neuronal activity, recorded over extended spatial areas using microelectrode arrays, have demonstrated the importance of considering seizure activity in terms of two distinct spatial regions: the ictal core and penumbral territories. The pathological information latent in these two areas is likely to be very different. We investigated therefore whether units could be followed reliably in these two areas. We isolated unit recordings from several hundred neurons from five patients undergoing video-telemetry monitoring for surgical evaluation of focal neocortical epilepsies. Unit stability could last in excess of 40 hours, across multiple seizures. In the penumbra, spike stereotypy was maintained even during the seizure. Penumbral firing showed a general increase in firing rate, though with very variable activity, including a subset of cells showing decreased firing. In contrast, within the ictal core (a region characterized by intense hypersynchronous multiunit firing) our spike sorting algorithms fail as the units were incorporated into the seizure activity, until the end of the seizure, but recovery of the spike shape was rapid following seizure termination, including changes in spike shape. Post-ictal firing rate within cells was equivalent to pre-ictal levels, suggesting that the common post-ictal loss of consciousness is a trait of network activity as opposed to anticipated alterations at cellular levels. In territories recruited to the ictal core, cells showed stereotypically infrequent activity for many hours even after clinically defined seizure termination, including an increase in mutual information and single cellular firing patterns atypical of known states of consciousness.

Poster Ref: P3-F-045

Theme: F: Nervous System Disorders

Investigating cognitive dysfunction to improve outcome in a mouse model of post-traumatic stress disorder.

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The persisting emotional dysregulation that arises following traumata is exacerbated by stress, as is found in post-traumatic stress disorder (PTSD). Fear memory generalisation, where related stimuli elicit a fearful reaction, is a common phenomenon in PTSD that contributes to poor quality of life. We hypothesise that generalisation arises from cognitive processing that is disturbed by chronic stress and that fear memory specificity predicts the efficacy of extinction-based therapies.

Adult male c57bl6j mice underwent chronic stress (one hour immobilisation stress daily for seven days) and were compared to non-stressed conspecifics. We exposed mice to a conditioned stimulus tone (CS+, 2 kHz) that was paired with a foot-shock (0.35 mA) during Pavlovian fear conditioning. The freezing to the CS+ and to unpaired tone stimuli (CS-1, 6 kHz; CS-2, 10 kHz) was assessed following fear extinction training. We found that fear memory re-emerged 21-28 days following fear memory extinction, and that this coincided with fear memory generalisation in chronically-stressed mice compared to controls. Analysis of immediate early gene expression in projection neurones to the amygdala revealed a role for a thalamo-cortico-amygdalar circuit in fear generalisation. We also assessed functional connectivity between thalamic nuclei and the lateral amygdala, which appears to be related to the specificity of auditory fear memory.

Together, these data suggest that chronic stress induces changes in thalamo-cortico-amygdalar circuit activity that diminishes the specificity of a fearful memory, and thus, gives rise to generalisation. Fear memory generalisation coincides with the re-emergence of fear memory following its extinction. The dysfunctional cognitive processing of this circuit provides a target by which the specificity of a fear memory may be modulated to improve the efficacy of extinction-based therapies in PTSD and anxiety disorders.

Poster Ref: P3-F-046

Theme: F: Nervous System Disorders

Evaluation of behavioural tests to identify early phenotypic changes in P301S Tauoupathy mice.

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Tau is a highly soluble cytosolic microtubule binding protein which, under pathological conditions, forms neurofibrillary tangles (NFT) containing hyperphosphorylated Tau. Intracellular accumulation of these NFTs is believed to lead to synaptic loss and neuronal cell death. Therefore, compounds that directly or indirectly attenuate Tau aggregation hold promise to treat Tauopathies in *e.g.* Alzheimer's disease (AD) or frontotemporal dementia. To evaluate *in vivo* efficacy of such treatments, rodent models are needed where Tau aggregation can be correlated to a sensitive behavioural phenotype.

P301S mice are a commonly used Tauopathy model showing muscle weakness, tremor and severe paralysis at 6 months. In this study, we evaluated age-dependent motor dysfunction in P301S mice using a battery of tests including grip strength, inverted screen, walking beam and rotarod.

Female P301S and C57BL6 control (WT) mice were investigated in the battery from 2 to 5 months of age, either naïve or repetitively once a month. Clasping behaviour and paralysis was scored referring to functional loss of hind paws. Muscle strength was measured using fore paw grip strength and inverted screen at which animals were observed for their ability to climb to the top of an inverted grid. Balance was monitored using the walking beam test, measuring the time to reach a platform at the end of either side of a horizontal bar. Rotarod performance was evaluated on a rotating rod and time of first turnaround and falling off was measured.

Analysis of data revealed gradual decrease with age in WT animals in inverted screen and walking beam. Repeated testing had minor impact: although walking beam was gradually impaired and an improved performance in rotarod was shown. Clasping behaviour was observed in P301S animals at 3-4 months progressing to paralysis at 5 months in some of the animals. All tests showed gradual decrease with age in P301S animals with impairment at 4-5 months compared to WT.

Although tau pathology in P301S mice starts at 3 months of age, general functional impairments were shown with short delay suggesting a causative relationship between Tau aggregation and the observed phenotypic changes. More work needs be done to confirm this relationship.

Poster Ref: P3-F-047

Theme: F: Nervous System Disorders

Altered cortical excitability of the ipsilateral hemisphere in frontal lobe epilepsy.

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Background: Previous studies of Transcranial Magnetic Stimulation (TMS) in focal epilepsy have shown altered cortical excitability measures such as motor threshold (MT), cortical silent period (CSP), short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF). These differences may be dependent on stimulus intensity. However, results have been conflicting, possibly due to high intersubject and interobserver variability in heterogenous studies of focal syndromes, with little correlation between parameters. It remains to be determined whether cortical excitability is altered in the hemisphere containing the seizure focus.

Methods: TMS data were examined from 12 subjects with chronic frontal lobe epilepsy on anticonvulsant therapy, and 11 matched controls. CSP durations and MEP amplitudes were measured at stimulus intensities of 130%, 150% and 175% of active MT, as well as paired pulse parameters of SICI and ICF thresholds. Methods to reduce intersubject and interobserver variability were utilised together for the first time in intergroup comparison.

Results: MEP amplitude was decreased in the ipsilateral hemisphere of patients at intensities of 150% and 175% (150% $P<0.001$, 175% $P=0.028$) compared to controls. CSP duration was increased at 130% ($P=0.035$). However, correcting for variability using the ratio of CSP / MEP demonstrated differences in the ipsilateral hemisphere at all intensities (130% $P<0.001$, 150% $P=0.008$, 175% $P=0.015$), with no difference in the contralateral. An increased active MT was found in both hemispheres, which was strongly correlated with decreased and SICI and ICF thresholds.

Conclusions: This provides further evidence of altered cortical excitability in the hemisphere ipsilateral to the seizure focus, in a homogenous cohort of frontal lobe epilepsy and supported by methods to reduce the variability of TMS. The global differences in thresholds may represent the medication effects or physiological changes distal to the seizure focus. However, the hemispheric asymmetry observed with CSP/MEP cannot be explained by therapy alone and most likely represents altered cortical pathophysiology in the hemisphere containing the seizure focus. Further study in a drug naïve cohort would dissociate the effects of medication.

Poster Ref: P3-F-048

Theme: F: Nervous System Disorders

Treatment of spasticity in a mouse model of spinal cord injury using VSN16R.

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Spinal cord injury (SCI) leads to major neurological impairment. Over the first 1 or 2 years post-injury, patients succeed in making remarkable adaptations to their expectations from life and learn to live a much altered but satisfying life within the limitations of their functional loss. However, a number of debilitating complications can further reduce the quality of this new adapted life. These can include chronic pain, bladder dysfunction, bowel dysfunction, autonomic dysreflexia, sexual dysfunction and also spasticity, which can lead to muscle pain. We have used a mouse model of SCI to test the efficacy of a newly developed drug as a treatment for post-SCI spasticity. Adult outbred CD1 mice were spinal cord injured using standard procedures to cause thoracic contusion or compression injuries. During the immediate recovery phase and afterwards (up to 10-12 weeks), animals were monitored for signs of hindlimb spasticity. Hindlimb spasticity was assessed using a visual scale adapted from the Ashworth Scale used in humans to monitor spasticity. Animals showing clear signs of spasm were filmed responding to movement in extension and the severity of the response assessed. Animals were treated orally with VSN16R (R(+)-3-(5-dimethylcarbamoyl-pent-1-enyl)-N-(2-hydroxy-1-methyl-ethyl)benzamide (5 mg/kg), a novel anti-spastic compound developed for the treatment of spasticity in multiple sclerosis. Following oral delivery of the compound, animals demonstrated a clear decrease in hindlimb spasms within 15-30 min post administration, compared to vehicle treatment. This occurred in the absence of any obvious signs of sedation. Sedation is the factor which limits the use of current anti-spastic treatments in humans. VSN16R has over a thousand fold therapeutic window in rodents and is safe and very well tolerated in healthy volunteers. This may provide a new drug candidate for treating spasticity in SCI in man.

Poster Ref: P3-F-049

Theme: F: Nervous System Disorders

Anterior cingulotomy for major depression does not impair stroop task performance but depression severity does.

Serenella Tolomeo[1], Ines Jentzsch [2], Christine Matthews[1], Keith Matthews[1] and J. Douglas Steele[1]

[1]University of Dundee, [2]University of St Andrews

Introduction: Neuropsychological impairment on the Stroop task – a classic neuropsychological task measuring the effect of interference on attention and reaction time - has been consistently demonstrated in patients with depression (Epp, 2012). Extensive anterior cingulate cortex damage in non-depressed humans is also associated with impairments on the Stroop task (Ochsner, 2001). Anterior cingulotomy (ACING) is a neurosurgical therapy for treatment-resistant depression (TRD) and involves the creation of bilateral lesions in the dorsal anterior cingulate cortex. It is not known whether patients who receive this treatment show impairments on Stroop performance. We therefore tested the hypothesis that mood and ACING would induce deficits (increased errors and slower responses) on the Stroop task.

Methods: Brain structure and neuropsychological functioning were investigated in 15 patients with a diagnosis of TRD who received ACING, 20 matched TRD patients who had not received ACING (TRD), and 20 healthy, never-depressed controls (all matched for age, IQ and gender). T1 weighted Magnetic Resonance Images were acquired.

Results: Both ACING and TRD groups showed performance deficits when compared with controls on the emotional and classical Stroop tasks. However, the ACING group did not show greater performance deficits than the TRD group. The number of correct responses and errors were highly correlated with clinical ratings of depression severity in both ACING and TRD groups. Patients who had received ACING and made a good recovery following surgery performed similarly to controls. The Stroop reaction time effect, which involves slowing on incongruent trials, correlated with white matter reductions in the anterior cingulate cortex. Increased reaction times strongly correlated with white matter reductions in the amygdala/hippocampal complex, a region implicated in TRD, but presumed unaffected by ACING.

Conclusion: This study supports the interpretation that ACING does not impair Stroop performance, but that depression (TRD) does. This may be because the ACING procedure produces small, discrete lesions compared to extensive medial prefrontal damage previously described in the literature which is associated with Stroop task impairment.

Poster Ref: P3-F-050

Theme: F: Nervous System Disorders

Reward prediction under uncertainty in depression.

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Human decision-making is often not optimal. Various cognitive biases are usually attributed as being the cause of sub-optimal decisions. For example, the optimism bias makes people overestimate probabilities of future rewards. In our previous work we showed how the optimism bias influences reward prediction in cases of uncertainty. Interestingly, optimism has previously been reported to be linked to clinical questionnaire scores in major depressive disorder . In the present study, we extend our work by comparing reward estimation under uncertainty between healthy controls (N=20) and non-medicated participants with depressive symptoms (N=20; satisfying ICD-10 depression diagnosis criteria) in a two-alternative forced choice behavioural task.

We here focus on behavioural findings. We found that the task performance of depressed participants was impaired. In particular, their behaviour differed from healthy controls when it came to comparing estimates of low reward predictors. Depressed participants under-estimated values of stimuli that predicted rewards more often. On the other hand, they were just as good as healthy subjects at estimating values of low reward predictors. Using Bayesian modelling, we found that all participants over-estimated probabilities of future reward and this tendency correlated positively (ρ=0.389, p=0.013) with their trait optimism scores and negatively with their pessimism (as measured using the LOT-R questionnaire, ρ=-0.419, p=0.007) and anxiety symptoms scores (as measured using the BDI questionnaire, ρ=0.439, p=0.005). However, this correlation was markedly more expressed in healthy controls than in depressed participants.

Our present results suggest that participants with depression have decreased valuation of positive events. This suggests that the optimism bias has little to no effect on estimating the likelihood of future rewards in depression, which presents a novel avenue for future investigations into how depression works.

Poster Ref: P3-F-051

Theme: F: Nervous System Disorders

Compartmentalisation of dysfunctional mitochondrial metabolism in experimental diabetic neuropathy.

Oliver Freeman, Richard Unwin, Andrew Dowsey, Paul Begley, Sumia Ali, Katherine Hollywood, Nitin Rustogi, Rasmus Petersen, Warwick Dunn, Garth Cooper and Natalie Gardiner

University of Manchester

The terminals of human PNS neurons can be up to a metre away from their cell body and the regulation of metabolism throughout this length is a challenging feat. This feat appears important in peripheral neuropathies – such as those associated with diabetes, chemotherapy and HIV – where distal limbs, innervated by the longest axons, are most affected. We explored the regulation of metabolism in different compartments of the sciatic nerve in streptozotocin (STZ)-diabetic rats compared to saline-injected controls. After 12 weeks of hyperglycaemia, STZ rats showed a neuropathic phenotype with decreased hindpaw innervation and decreased sciatic nerve conduction velocity. Using untargeted proteomics (control n=4, diabetic n=6) and metabolomics (n=10), we characterised the sciatic nerve (SN) – the distal axonal compartment – and the lumbar 4/5 dorsal root ganglia (DRG) – the proximal cell body compartment. In the SN, 28.9% of the 2,356 proteins identified had significantly altered expression in diabetes but only 5.2% of 1,649 proteins changed in the DRG. Proteins within oxidative phosphorylation and glycolysis were particularly affected in the SN, with expression unaffected in the DRG. In oxidative phosphorylation, 32/37 (86%) proteins were significantly upregulated in the SN whilst not one of these proteins changed significantly in the DRG. Metabolomics revealed that this was not due to altered glucose distribution/utilisation. Both tissues contained a similar proportion of significantly altered polar metabolites (20/55 in the SN, 16/53 in the DRG) and higher concentrations of glucose, fructose and sorbitol in diabetes. Analysis of non-polar lipid metabolites supported differential metabolic dysfunction with 65.9% of 278 lipid features significantly altered in the SN in diabetes (notably triacylglycerols and acylcarnitines), but just 5% of 338 lipids changed in the DRG. These results indicate that despite altered glucose utilisation in both the SN and DRG, the molecular consequences are more marked in the SN. The peripheral nerve compartment, comprising largely of axons and Schwann cells, appears more susceptible to mitochondrial dysfunction. The deleterious consequences of this may contribute to the distal pathology of the disease.

Poster Ref: P3-F-052

Theme: F: Nervous System Disorders

The amygdala plays in stereo to recruit the ventral-to-dorsal striatal transitions in the control over cocaine seeking habits.

Aude Belin-Rauscent[1,2], Jennifer E. Murray[2,3], Marine Simon[4], Chiara Giuliano[2,3], Marianne Benoît-Marand[5], Barry J. Everitt[2,3] and David Belin[1,2]

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Addiction may result from loss of executive control over maladaptive drug seeking habits. At the neurobiological level, the transition from volitional to habitual cocaine seeking behaviour depends upon a shift from a network involving the nucleus accumbens core (NAcC) and its functional interactions with the basolateral amygdala (BLA) to a network involving dopaminergic projections to the dorsolateral striatum (DLS).

If the mechanisms whereby these intrastriatal shifts occur are now better understood, nothing is known about the neural systems by which they are triggered.

Since the BLA projects to the NAcC and not the DLS, we hypothesised that it is through this projection, and subsequent activation of serial connections *via* midbrain dopamine neurons, so-called dopamine striato-nigro-striatal circuitry, to influence the DLS, that DLS-dependent habitual cue-controlled drug seeking is engaged by associative mechanisms in the amygdala. However, the BLA also projects to the central nucleus of the amygdala (CeN) – which in turn projects to the substantia nigra innervating the DLS – so providing an alternative route to influence DLS processing.

Combining functional disconnections and electrophysiological recordings of the amygdalo-striatal networks in rats, we investigated the two possible routes by which the amygdala may trigger the functional recruitment of DLS control over cocaine seeking behaviour when it becomes habitual.

Functional disconnections demonstrated that both the BLA and the CeN are necessary to recruit DLS dopamine dependent cocaine seeking habits. Using *in vivo* extracellular electrophysiological recordings we then demonstrated that the BLA exerts functional control over the activity of medium spiny neurons (MSNs) in the DLS through a polysynaptic network that involves glutamatergic mechanisms in the NAcC. The NAcC having no reciprocal projections with the CeN, these data suggest that the control exerted by the BLA over the function of MSNs in the DLS may involve striato-nigro-striatal loops linking functionally the NAcC to the DLS.

These data demonstrate that the BLA and CeN are both required, through parallel circuitries, to trigger the development of dorsolateral striatum dopamine-dependent cocaine seeking habits.

Poster Ref: P3-F-053

Theme: F: Nervous System Disorders

Mechanisms of IL-1 signalling under disease-relevant conditions.

Michelle Edye, Stuart Allan and David Brough

University of Manchester

In recent years it has become clear that inflammation plays a major role in CNS disorders. Interleukin-1 is a pro-inflammatory cytokine that drives inflammation and has been shown to exacerbate a number of CNS disorders including: stroke, Alzheimer's disease, epilepsy and traumatic brain injury [1]. However, the mechanisms of IL-1 signalling under disease conditions are relatively unknown. The microenvironment changes during insult or injury and often oxygen supply does not meet demand so a period of acidosis is experienced. Here we looked at IL-1 signalling under disease related conditions (acidosis).

Activation of IL-1β is a two-step process. A first signal is required to induce synthesis of the inactive pro-form of IL-1β followed by a second signal to induce its cleavage to an active form. The protease responsible for this second activating cleavage is classically described as being caspase-1. However, a number of other proteases have also been found to cleave IL-1β at various locations and play a role in disease [2].

The activity of mature IL-1α and β at neutral and acidic pH was determined using a HEK-IL-1 reporter assay. Previous work has shown a cathepsin-D cleaved 20 kDa IL-1β to be produced under acidic conditions but the activity of this, or other forms of IL-1β, under acid conditions has never previously been measured. This work provides valuable information on IL-1 signalling under disease conditions which could be used to help direct drug discovery programs aimed at treating inflammatory diseases.

[1] S. M. Allan, P. J. Tyrrell, and N. J. Rothwell, "Interleukin-1 and neuronal injury," Nat. Rev. Immunol., vol. 5, pp. 629–640, 2005.

[2] M. G. Netea, F. L. van de Veerdonk, J. W. M. van der Meer, C. A. Dinarello, and L. A. B. Joosten, "Inflammasome-Independent Regulation of IL-1-Family Cytokines.," Annu. Rev. Immunol., Dec. 2014.

Poster Ref: P3-F-054

Theme: F: Nervous System Disorders

Optimal surgery prediction for temporal lobe epilepsy.

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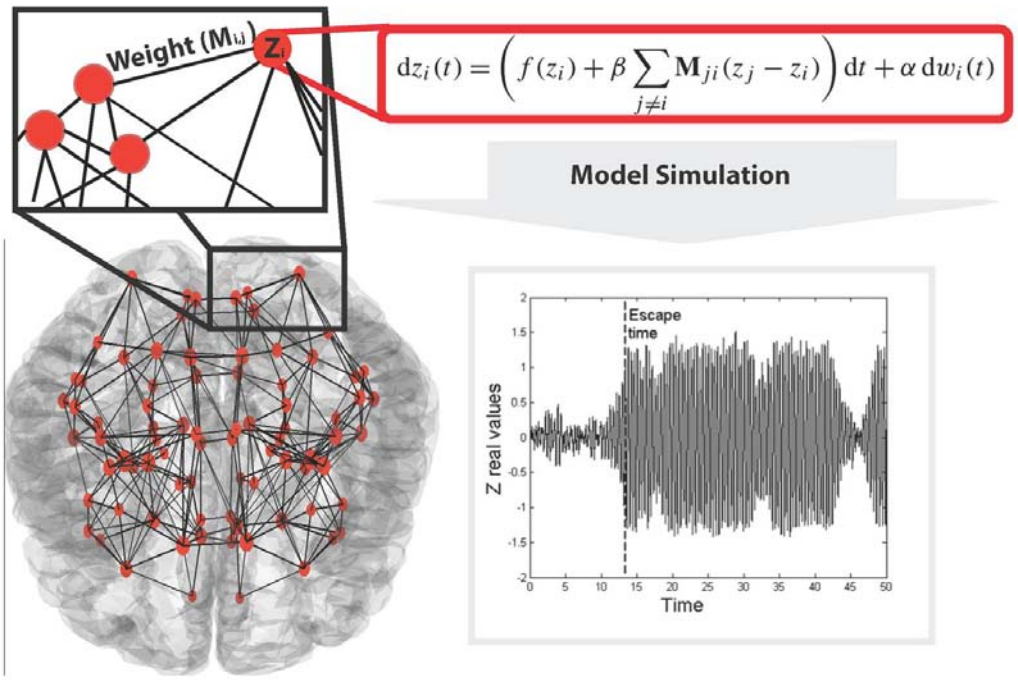
Newcastle University

Temporal lobe epilepsy (TLE) is a nervous system disorder that has been linked with changes in structural connectivity in the brain and associated with reduced surface area in various brain regions. In the case of drug resistant epilepsy resective surgery is often considered; a procedure hampered by unpredictable success rates and traumatic for patients. The aim of this study is to work towards improving surgery success rates with a predictive computational model.

This poster shows the application of a bistable model of epilepsy to patient specific full brain networks. The patient data was acquired through connectome creation from diffusion tensor imaging (DTI) and functional magnetic resonance imaging (fMRI) of 22 left TLE patients and 39 controls. The model was tested by looking for patient-control differences in seizure onset time and origin location.

The potential of this model for surgery prediction was assessed by carrying out *in silico* surgical resections, removing nodes from patient networks and comparing seizure likelihood post-surgery to pre-surgery simulations. Resection of clinically removed regions in this model found better success rates - comparable to surgery results in reality - than random resections. Additionally, individualised surgery predictions were found for each patient which when resected significantly reduced seizure likelihood in 16 out of 22 patients. These results predict surgery success rates of individuals which can then be compared to reality. The future aim is to predict alternative optimal surgical procedures for patients with a low predicted likelihood of success for standard surgery procedures.



The model workflow – from patient connectivity networks to simulations by application of a mathematical model.

Poster Ref: P3-F-055

Theme: F: Nervous System Disorders

Evaluation of PET tracer [11C]PBR28 as a marker for microglial activation in the 5xFAD mouse model of Alzheimer's disease.

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The role of microglia has become a major focus of Alzheimer's disease (AD) research. Progress has been hampered by the inability to follow the development of astrogliosis and microgliosis longitudinally, to assess whether there is any correlation with changes in behaviour and cognition. For over 2 decades, the PET radioligand [^{11}C]-R-PK11195 has been widely used to image the mitochondrial translocator protein (TSPO), which is associated with activated microglia. Yet accurate quantification of microglial density using [^{11}C]-R-PK11195 has been challenging due to the limitations of the ligand. [^{11}C]PBR28 is a recently developed TSPO PET ligand with improved signal to noise ratio, and therefore we sought to evaluate whether [^{11}C]PBR28 is suited to study microglial activation in a transgenic mouse model of AD. Transgenic mice (5xFAD, 6 months old, n=4) and their corresponding control wild-type (WT) mice (C57BL6, 6 months old, n=4) were scanned using a Siemens Inveon small animal PET/CT scanner following [^{11}C]PBR28 intravenous administration, and dynamic PET data was acquired. A subset of the 5xFAD mice (n=3) and a corresponding WT mouse each underwent two separate scans (24 hours apart) to assess the test-retest variability. PET- and CT-driven regions of interest were defined in the brain and heart and regional time activity curves (TAC) generated. The average standard uptake value (SUV) between 30 and 60 min and the area under the TACs (AUC) were calculated. The brain SUV and AUC were normalised to the heart SUV and AUC. Finally, the intra-subject variability (relative difference, ΔR) between test and retest was calculated. Normalised brain SUV and AUC in the 5XFAD mice (SUV:0.384±0.057; AUC:0.337±0.033) was significantly higher ($P<0.01$) compared to that in the WT controls (SUV:0.285±0.030; AUC:0.262±0.023). The normalised brain AUC showed good test-retest variability with ΔR ranging from 0 to 13% for the 4 mice that were scanned twice. We found an increase in brain uptake of [^{11}C]PBR28 in the 5XFAD mouse model compared to the control WT mice, suggesting an increase in microglial activation in models of AD. Autoradiography using [^{3}H]PBR28 and immunohistochemistry using an antibody against Iba1 were performed on brain sections from the scanned WT and 5xFAD mice.

Poster Ref: P3-F-056

Theme: F: Nervous System Disorders

Investigating the structure-function relationship of somatosensory dendritic spines in a model of Fragile X Syndrome.

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Autism spectrum disorders (ASDs) and intellectual disabilities (IDs) are neurodevelopmental disorders typified by cognitive deficits, sensory and behavioural dysfunction. ASD/ID syndromes arise due to genetic, environmental or idiopathic mechanisms, which can be capitulated through monogenic mutation. The synaptopathic ASD/ID, Fragile-X syndrome (FXS) arises from reduced expression of the Fragile-X Mental Retardation Protein, accounting for >20% of all monogenic ASD/IDs. The barrel cortex of rodents is known to receive tactile sensory input and represents a model network to assess FXS function.

However, while altered spine density and shape have been found, recent work from our lab (Wijetunge *et al.*, 2014), has contradicted this as FXS dependent dendritic spine deficits were not fully recapitulated when examined under super resolution microscopy, presenting a more subtle phenotype which varied between brain region and cell type. As structural properties of spine morphology are known to effect functional currents (Noguchi *et al.*, 2005, 2011; Tønneson *et al.*, 2013) it is possible that a prominent phenotype of FMRP loss is a breakdown of this relationship. We now show that a breakdown in the structure-function relationship may occur in developing S1. We show that while spine density and shape is largely unaffected during the postnatal week 2 (Till *et al.* 2012, Wijetunge *et al.* 2014) thalamically induced circuit activity is severely impaired. Furthermore, we and others (Gibson *et al.*, 2008) show decreased layer 4 reciprocal connectivity at this age. To elucidate the origin of this decrease in layer 4 network activity despite normal spine shape and density, we have combined whole-cell patch-clamp recordings in acute slices of barrel cortex with 2-photon uncaging of glutamate on identified dendritic spines, which were morphologically characterized with super resolution STED microscopy. In the mouse model of FXS we observe a large decrease in thalamically-induced circuit activity despite largely normal spine structure and density. This study highlights a structure-function correlation for dendritic spines altered in transgenic models; hence caution should be exercised interpreting spine morphology in the absence of functional data.

Poster Ref: P3-F-057

Theme: F: Nervous System Disorders

Very fast oscillations recorded during intraoperative subdural electrocorticography as a prognostic marker for temporal lobe epilepsy surgery.

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Temporal lobe epilepsy with mesial temporal sclerosis (MTS) is one of the most common surgically treatable epilepsies. Refractory MTS can be treated by anatomically standardized en bloc resections such as corticoamygdalohippocampectomy (CAH). Although, some patients still present with seizures after the procedure. Several studies have reported the importance of very fast oscillations (VFO; >80Hz) as a reliable biomarker for detecting the epileptogenic foci. However, few studies report VFO in intraoperative subdural electrocorticography (ECoG). To investigate the prognostic significance of VFO recorded during intraoperative ECoG, 17 patients (age at surgery: 11-51; 64% female; 64% left focus) who underwent CAH to treat refractory MTS were evaluated. The ECoG was recorded at three different surgical times. The first recording session was performed prior to brain resection, the second after the corticotomy but before the amygdalohippocampectomy, and the last after the entire resection procedure. All recordings were made with 32 platinum electrodes (4mm diameter), the sample rate was 1 kHz, and recording sessions lasted an average of 10 minutes. The detection of VFO was performed by semi-automatic algorithms, i.e., every candidate event were reviewed in visual inspection aiming to eliminate possible filtering artefacts, in two interesting band: Ripples (Rp; 80-200 Hz) and Fast Ripples (FRp; > 200 Hz). Postoperative outcome was assessed using the “Engel Epilepsy Surgery Outcome Scale” two years after the procedure. We were able to detect VFOs in intraoperative ECoG despite the limitations of the technique , including short recording time, influence of anesthesia, and presence of artefacts. The majority of events were observed in the first recording session, especially in basal cortex followed by the second session in the hippocampal electrodes. Also, the ratio FRp/Rp in the basal cortex and hippocampus of patients who did not become seizure free after the procedure are lower than in Engel 1a patients. This may indicate that the epileptic network is more distributed in these patients. These findings suggest reappraising intraoperative subdural ECoG recordings as a tool for MTS surgery, using the VFO as a prognostic marker.

Poster Ref: P3-F-058

Theme: F: Nervous System Disorders

The De-Caff study: caffeine in dementia.

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Background: Attentional fluctuations are one of the cardinal features of Dementia with Lewy Bodies (DLB). Attention is traditionally separated into three distinct but interacting anatomical networks – alerting, orienting and executive. Caffeine is a widely used stimulant that may improve certain subtypes of attention in patients with DLB, although this has not been investigated. In this study we explore whether caffeinated, compared to decaffeinated, coffee will improve performance on experimental and real-world tasks of attention in healthy elderly controls and participants with DLB.

Methods: A double blind, placebo-controlled, cross-over design was chosen to detect the effects of caffeine on attention. The alerting network was assessed by simple and choice reaction times, the orienting network by a rapid serial visual presentation (RSVP) paradigm and the executive network by a Stroop task. The Walking and walking while talking (WWT) task acted as functional measures of attention. The tests of attention were repeated over a nine day period on the first, seventh, eighth, and ninth day. Day 1 served as a baseline assessment of attention on habitual caffeine intake. This was followed by 1 week of caffeine abstinence and testing on day 7 as a post-withdrawal baseline. On Day 8 participants were assigned to the blinded, counterbalanced 'Caffeine' or 'De-caffeinated' condition and provided a drink 1 hour prior to testing. On Day 9 the alternate drink was received. Sleep and caffeine foodstuffs questionnaires were completed daily during the trial. Testing was conducted at the same time on each day to account for normal circadian fluctuations in attention.

Results: Preliminary 10 healthy elderly participants suggest caffeine has no benefit on tests of attention or the simple walking task. However, in 9 participants who completed the complex WWT task a caffeinated (M = 11.69 (s), SD = 2.64) drink yielded a significantly faster time than a decaffeinated drink [M = 12.26 (s), SD = 2.55, t(8) -3.42, p = .009]. Future testing will include DLB participants.

Conclusion: Preliminary data suggest that caffeine significantly improves a real-world test of attention and should be investigated further, particularly as impaired WWT is associated with risk of falls in elderly people.

Theme G: Methods and Techniques

Posters P3-G-001 to P3-G-014

Poster Ref: P3-G-001

Theme: G: Methods and Techniques

An automated approach for two-photon targeted recordings *in vivo*.

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Understanding the functional principles of the mammalian cortical circuit is one of the major projects of modern neuroscience. To make progress on this problem, we need to be able to observe the behaviour of the individual neuronal elements of this circuit. The whole cell patch clamp technique has been the 'gold standard' method for this, as it allows both subthreshold and suprathreshold electrical signals to be recorded. Recently, Kodandaramaiah *et al.* (Nature Methods 9:585-7, 2012) developed an automated approach for performing blind, *in vivo* patch clamping. Now, by targeting this technique to specifically labeled individual cells or cell classes (Margrie *et al.*, Neuron 39:911-8, 2003), it may be possible to test a wide range of hypotheses concerning information processing operations performed by the cortical circuit. To make this possible, we have developed a strategy for two-photon targeting of an automated whole cell patch clamping algorithm. Our Robotic Integrated Targeted Autopatcher (RITA) is responsible for the control of a micromanipulator, a custom made electromechanical regulator for glass electrode internal pressure control, a microelectrode signal amplifier and a two-photon microscope. Images of fluorescently labelled neuronal tissue are acquired through the two-photon microscope, targets for patch clamp are selected *via* a point-and-click graphical user interface. Optical coordinates converted into the micromanipulator coordinate system, and then a suitable path calculated to guide the patch pipette towards the target. Our system allows us to compensate for brain tissue deformation and subsequent neuronal target movement caused by pipette insertion. RITA is currently being tested and calibrated for targeting specific cell classes in the cortex of the intact mouse brain labelled *via* either fluorescent dye loading (*e.g.* Oregon Green BAPTA-1) or genetically-encoded indicators (*e.g.* GCaMP6). The strategy at the core of RITA naturally scales to the selection of multiple identified neurons, and may thus permit simultaneous targeted patch clamp recordings from neuronal ensembles.

Poster Ref: P3-G-002

Theme: G: Methods and Techniques

Circuit based genome editing using Attenuated Rabies Pharmacologically Activatable (ARPA).

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Understanding how neurons are organized in neuronal networks, compute and integrate information and generate specific behaviours, is one of the main focus of neuroscience. The connectivity between neurons can be addressed through chemical or viral neuronal tracing.

Among all the neurotropic viruses that can spread trans-synaptically, the Rabies virus is the most effective. It can be engineered to spread retrogradelly mono-synaptically. The deletion of the spike glycoprotein G from the Rabies genome (ΔG-Rabies) generates a functional virus unable to spread. This virus can be used as retrograde mono-synaptic tracer by providing in trans the Rabies glycoprotein in the primary infected neurons.

Although the ΔG-Rabies has been widely used to perform neuronal tracing, as all the viral trans-synaptic tracers, it is a replicative competent virus that kills the cells in less than 2 weeks.

Therefore, it is not possible to perform long term trans-synaptic tracing and to address the contribution of specific synaptically connected neurons to behaviours, memory or learning.

To overcome this limitation we decided to modify the ΔG-Rabies to create a new generation of attenuated mono-synaptic tracers.

Since the deletion of viral proteins other than G from the Rabies genome impairs its ability to complete the life cycle, we decided to affect the viral protein stability instead of replacing them. Each Rabies protein was individually tagged with a small and effective degradation domain. The degradation domain was fused through a linker containing a cleavable site recognized by a specific inducible protease, which was cloned in the G locus of these viruses.

Thus, a series of viruses in which the stability of different viral protein is regulated exogenously by drug addiction was generated. We showed that the inducible protease cassette inside the Rabies genome is functional *in vitro* and *in vivo* and we investigated how the destabilization of different viral proteins affects the viral production.

These viruses pave the way to study the contribution of specific circuits to behaviour, to the selective manipulation of gene expression in a circuit specific manner and to study circuits' rearrangements upon learning.

Poster Ref: P3-G-003
Theme: G: Methods and Techniques

Can we measure the human mirror neuron system with EEG?

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University of Oxford

Mu activity is rhythmic EEG activity (8-12 Hz) recorded from sensorimotor cortex. The mu rhythm is suppressed when performing an action, and when observing another person's actions, and has therefore been proposed as a signature of the activity of the human mirror neuron system (MNS). Mu suppression is already being widely used in social cognitive neuroscience as a measure of MNS activity, and it has been suggested as a target for neurofeedback in individuals with autism spectrum disorders. However, mu suppression suffers from several methodological problems. The mu frequency band overlaps with the alpha frequency band, and as alpha is sensitive to attentional fluctuations it is unclear to what extent mu suppression is confounded by changes in attentional engagement. The specific baseline against which mu suppression is assessed may be crucial, yet there is little consistency in how this is defined. Furthermore, previous research suggests that beta activity (oscillations around 13-35 Hz) is a better index of the involvement of motor cortical areas.

We will present preliminary data from an ongoing project that examines EEG oscillations at both the central and occipital electrodes while viewing motor movements (movements that do and do not involve manipulating an object), with a view to understanding further the involvement of attention and alpha activity in mu suppression. We are also comparing three different methods of baselining, and examining the responsivity of beta to explore the notion that beta may be a better index of mirror neuron involvement. This study is being conducted as a Registered Report, in which the aims, methods, and data analysis are pre-specified before the data is collected. This study therefore represents a large, robust and transparent investigation of mu suppression as a valid measure of the mirror neuron system.

Poster Ref: P3-G-004

Theme: G: Methods and Techniques

Studying the neural correlates of 'smoking' with e-cigarettes and fMRI: A feasibility study.

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Objective: The behavioural and sensory features of smoking are an important aspect of maintaining cigarette addiction, but have been poorly studied. This is likely due to practical and safety issues associated with the use of combustible materials in the modern laboratory environment. Electronic cigarettes may obviate these problems. The aim was to test the feasibility of using e-cigarettes in (f)MRI studies of 'smoking'.

Methods: Initial scans were performed with a MRI phantom, and one participant (author MW) in order to assess different brands of e-cigarette for safety and effect on MR image quality. Several brands were identified which contained no ferrous metal, and had no apparent effect on functional image quality. Following this testing, participants (N=11) completed a MRI session that included a 10-min visual-cued smoking fMRI task (20 trials, inter-trial interval jittered between 25, 30 and 35s). A custom optical device recorded the light output of the LED at the tip of the e-cigarette, and physiological data were also acquired.

Results: Initial results showed that the magnetic susceptibility (and the effect on image quality) of different brands of e-cigarettes varied widely, however several brands were deemed suitable for use in the MRI scanner. In the main experiment, strong activity was seen in the left dorsal (hand area) and lateral (face/mouth area) motor cortex, and right cerebellum. This presumably reflects the hand and oro-facial movements associated with smoking. A number of other regions also showed significantly heightened activity to smoking events including several thalamic and sub-cortical nuclei (putamen, ventral striatum), the medial paracingulate gyrus, and the anterior insula bilaterally. These may reflect other more sensory or physiological (flavour, reward processing) aspects of smoking.

Conclusion: We have demonstrated the broad feasibility of using electronic cigarettes in the MR environment, particularly for functional MRI studies related to smoking behaviour. We have also shown for the first time the brain regions involved in the sensory and behavioural aspects of smoking. E-cigarettes represent a promising new paradigm for the study of smoking, and the brain processes involved in addiction generally.

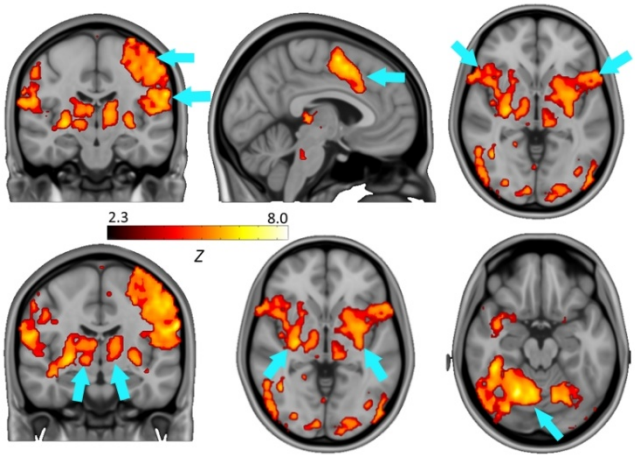

Figure 1. The neural substrates of the sensory and behavioural aspects of 'smoking' in cortical (top row, left-to-right; motor cortex, paracingulate gyrus, insula) and sub-cortical (bottom row, left-to-right; ventral striatum, putamen, cerebellum) regions. Activation maps thresholded at $z = 2.3$ ($p < 0.05$; cluster-corrected).

Poster Ref: P3-G-005

Theme: G: Methods and Techniques

Quantitative MRI study of neuroinflammation and its relationship to Interferon-alpha induced fatigue and depression.

Nicholas Dowell[1], Ella Cooper[1], Jeremy Tibble[2], Valerie Voon[3], Hugo Critchley[1], Mara Cercignani[1] and Neil Harrison[1]

[1]Brighton and Sussex Medical School, Brighton, [2]Brighton and Sussex University Hospital, Brighton, [3]Department of Psychiatry, University of Cambridge

Recent findings suggest that chronic systemic inflammation may play a part in the development of a number of neuropsychiatric disorders including depression and schizophrenia. Patients with hepatitis-C are often treated with the pro-inflammatory cytokine interferon-alpha (IFN-α). Though this (together with ribavirin) successfully clears the virus in many patients, most report severe fatigue and up to 1/3 symptoms indistinguishable from major depression. Quantitative magnetization transfer (qMT) is an MRI technique that provides information about the interaction of free water and macromolecular components of tissue. We investigated: 1) Whether the MT parameters: forward exchange rate (kf) and T2 relaxation time of free water (T2f) were sensitive to the subtle microstructural and metabolic effects brought about by IFN. 2) Whether these changes in microstructure predict the subsequent development of depression and fatigue. Nineteen hepatitis-C patients were recruited and scanned before and 4 hours after starting IFN-α therapy. Fatigue and depression were measured using a visual analogue scale for fatigue (fVAS) and the Hamilton depression questionnaire (HAM-D) at each time-point and for the remaining 6 months of treatment. Changes in kf and T2f were correlated against changes in depression and fatigue 4 weeks into treatment. The analysis was restricted to brain regions known to be implicated in depression (subgenual cingulate, amygdala) and the motivational changes associated with fatigue (basal ganglia, substantianigra/ventral tegmental area).

IFN-α was associated with overlapping changes in kf and T2f within the left basal ganglia and ventral striatum (Fig 1). Additionally, bilateral ventral striatal changes in T2f predicted the magnitude of fatigue experienced 4 weeks later ($p < 0.02$). By contrast, changes in depression were predicted by T2f changes in the substantia nigra ($p < 0.02$) and left-sided amygdala ($p < 0.05$).

This work demonstrates that qMT parameters kf and T2f are sensitive to acute effects of IFN on brain microstructure with changes observed within 4 hours of inflammatory challenge. Furthermore, regional changes in T2f appear to be predictive of both future depression and fatigue.

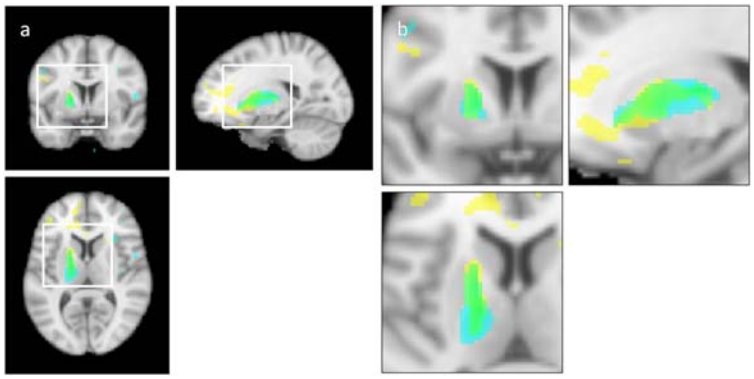

Fig 1 – Changes in qMT parameters kf and T2f, 4.5 hours after commencing IFN-α treat¬ment. The increase in kf (yellow) and decrease in T2f (cyan) are co-localized to left-sided basal ganglia and ventral striatum ($p < 0.005$ unc.), areas implicated in depression and fatigue.

Poster Ref: P3-G-006

Theme: G: Methods and Techniques

Extracellular N-acetylaspartate in human traumatic brain injury.

Richard Shannon[1], Susan van der Heide[1], Eleanor Carter[2], Ibrahim Jalloh[1], David Menon[2], Keri Carpenter[1] and Peter Hutchinson[1]

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Introduction: N-acetylaspartate (NAA) is an amino acid derivative primarily located in the neurons of the adult brain. The function of NAA is incompletely understood. The decrease in brain tissue NAA is presently considered symptomatic and a potential biomarker of acute and chronic neuropathological conditions. Here we have used microdialysis to investigate the behaviour of extracellular NAA (eNAA) levels after traumatic brain injury (TBI).

Methods: Cerebral microdialysis catheters (M Dialysis 71) were perfused at 0.3 µl/min. eNAA was measured in microdialysates by HPLC, in 22 patients with severe TBI, and, for comparison, in radiographically 'normal' areas of brain in 6 non-TBI neurosurgical patients. We established a temporal eNAA profile in 8 additional patients with severe TBI. Microdialysate concentrations of glucose, lactate, pyruvate, glutamate and glycerol were measured on an ISCUS clinical microdialysis analyser.

Results: The temporal profile of microdialysate eNAA was characterised by highest levels in the earliest time-points post-injury, followed by a steady decline; beyond 70 h post-injury average levels were 40 % lower than those measured in non-TBI patients. There was a significant inverse correlation between concentrations of eNAA and pyruvate; eNAA showed significant positive correlations with glycerol and the lactate/pyruvate (L/P) ratio measured in microdialysates.

Conclusions: The results of this on-going study suggest that changes in eNAA after TBI relate to the release of intracellular components possibly due to neuronal death or injury, as well as to adverse brain energy metabolism.

Poster Ref: P3-G-007

Theme: G: Methods and Techniques

The development of a method for acceptable and reliable extra-cranial detection of seizures in adults with epilepsy and intellectual disability.

Raj Seraya Bhatoa and Howard Ring

University of Cambridge

Epilepsy occurs often in adults with intellectual disability (ID). For those with an IQ below 70 the prevalence is around 30% and for those with profound ID the prevalence exceeds 50%. Many people with epilepsy and ID are unable to report when they've had a seizure and yet cannot be continuously observed by carers, especially at night, hence many seizures go unnoticed. Current assistive technologies such as bed mats to identify a seizure are limited in their applicability, sensitivity and specificity.

Various algorithms based on heart rate variability and accelerometry have been developed for seizure detection. Whilst these methods have been successfully used in preliminary investigations, they have not yet been combined into a single algorithm. The aim of this research is to develop a process and algorithm for detecting seizures in adults with ID and epilepsy, and to assess the acceptability to service users of our approach.

Based on the combined analysis of heart rate variability and accelerometry data we aim to develop methodology to support improved diagnosis of paroxysmal behavioural symptoms of unclear origin and to better monitor effects of antiepileptic medication in those with difficult-to-treat seizures. We aim to recruit 25 adults aged 18-65 with ID and epilepsy, each with a seizure frequency of 20 or more per month. Recordings of ambulatory EEG and physiological data comprising heart rate variability and accelerometry are required during two separate periods each lasting 72 hours. We aim to record data from a total of 100 seizures, a number consistent with those analysed in previous studies.

EEG data and carer records will be visually analysed to identify epileptic seizures. Features from heart rate variability and accelerometry data corresponding to seizure episodes will then be extracted, from 3 minutes pre-ictally to 3 minutes post-ictally. Features extracted from the data will be used to train classification algorithms, such as support vector machines. Data from 50 seizures will be used for training and data from another 50 seizures will be used to test the classifier. Sensitivity, specificity and positive predictive value of the classifier will be calculated.

Preliminary data associated with seizure occurrence will be presented.

Poster Ref: P3-G-008

Theme: G: Methods and Techniques

Tracking instantaneous phase of LFP for analyzing phase-amplitude coupling, cross-frequency coupling and spike-phase coding.

Taro Tezuka

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Phase-amplitude coupling (PAC), cross-frequency coupling (CFC), and spike-phase coding are increasingly recognized as playing fundamental roles in neural coding (1,2). One difficulty in analyzing them is that the frequencies of oscillations change over time. For this reason, the Hilbert transform is commonly used for estimating the instantaneous phase of LFP. However, if the signal is multi-component, that is, if there are more than one mode in the frequency domain, the Hilbert transform cannot find phases for each of these multiple modes (3).

One commonly used way to avoid this problem is to apply a narrow-band filter to the signal first and make it mono-component. Such pre-processing may have a demerit that one might lose track of the phase when the frequency deviates from the pass-band. Also, it is not clear how one can determine the width of the pass-band.

EMD (empirical mode decomposition) is another approach where one decomposes the signal into a set of simpler functions and estimates instantaneous phases for each one using the Hilbert transform.

We compared these methods using their abilities to detect spike-phase coding. We used CRCNS-hc2, a publicly available data set recorded from the hippocampus of a rat (5). We measured how spikes are sensitive to phase using curve fitting and compared the amounts of amplitude change in the fitted curves

[1] Lisman J, Buzsaki G (2008) A neural coding scheme formed by the combined function of gamma and theta oscillations. Schizophrenia Bulletin, 34(5):974-980
[2] Kayser C, Montemurro MA, Logothetis NK, and Panzeri S (2009) Spike-phase coding boosts and stabilizes information carried by spatial and temporal spike patterns. Neuron, 61(4):597-608
[3] Rilling G, Flandrin P (2008) One or two frequencies: the Empirical Mode Decomposition answers. IEEE Transactions on Signal Processing, 56(1):85-95
[4] Huang NE, Shen Z., Long SR, Wu MC, Shih HH, Zheng Q, Yen NC, Tung CC, Liu HH (1998) The empirical mode decomposition and the Hilbert spectrum for nonlinear and non-stationary time series analysis. Proceedings of the Royal Society of London A, 454(1971):903-995
[5] Mizuseki K, Sirota A, Pastalkova E, Buzsaki G (2009) Multi-unit recordings from the rat hippocampus made during open field foraging. http://dx.doi.org/10.6080/K0Z60KZ9

Poster Ref: P3-G-009

Theme: G: Methods and Techniques

Translational Neuroscience and Translational Psychiatry – Development of a new circuit-based framework.

Maria Dauvermann[1], Thomas Moorhead[2], Graham Lee[1] and Ki Goosens[1]

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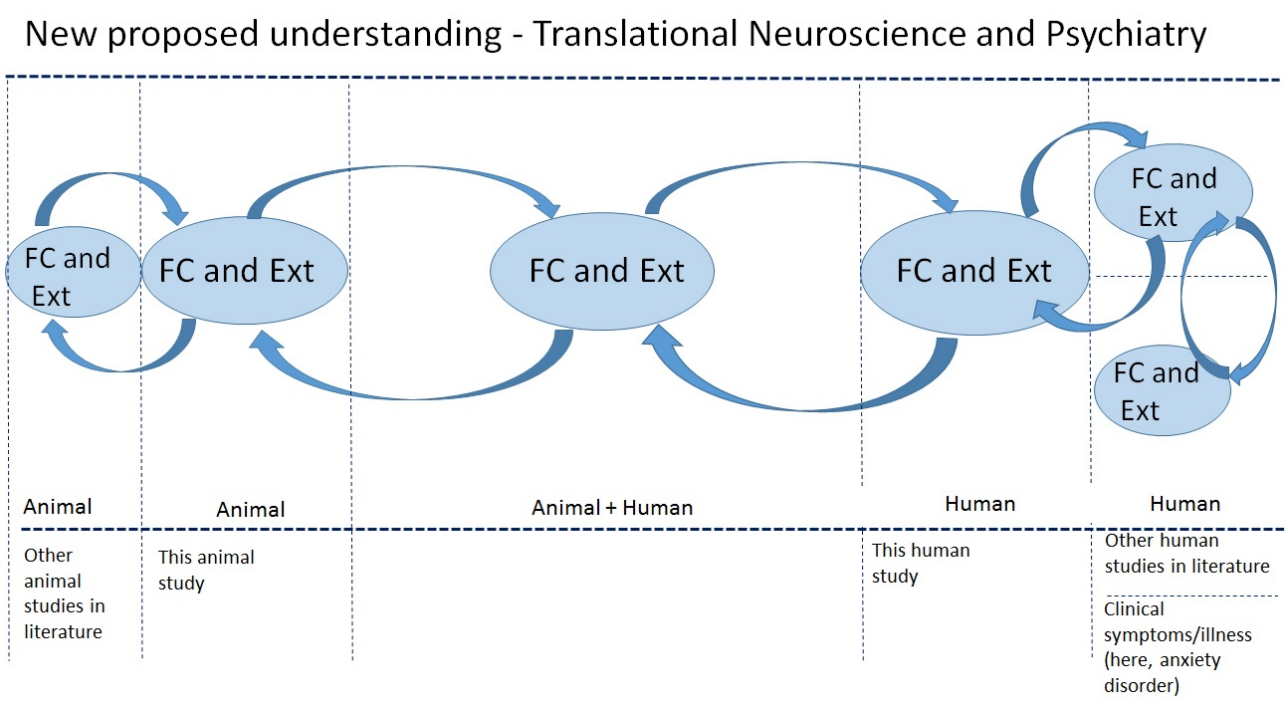
Background: Different approaches and frameworks of Translational Neuroscience (TN) and Translational Psychiatry (TP) have been proposed for gaining insight into pathophysiology of mental disorders. Examples include the design of animal models, the unidirectional translation from preclinical to clinical TN and TP, the design of experimental tasks between preclinical and clinical TN/TP, the unidirectional translation within clinical TN and TP and from clinical to preclinical TN and TP, and species translation). However, the majority of those concepts were developed for circumscribed research (sub)fields, experimental tasks, techniques and/or mental disorders. Thus, an integrating methodological framework for systematic application of translational steps for all neuroscientific fields and mental disorders is missing.

Methods: Previously defined factors for TN and TP have been adopted for the foundation of translational potential. Furthermore, fear conditioning as one of the established experimental tasks in preclinical TN and TP and clinical TN and TP (both in healthy controls and patients have been applied as described recently. Here, we used fear conditioning and extinction as an example of how the framework can be used for translation of a specific experimental task in any specific (sub)field in a specific mental disorder (anxiety disorder) and be integrated into other fields in TN/TP.

Results: We present a preliminary framework for TN and TP as a circuit-based process in order to improve translational potential to be employed in any research (sub)fields and/or mental disorders (Figure 1). This framework is based on the traditional understanding of TN and TP when considered as a circuit-based process.

Discussion: This framework can be used by every researcher in any field of TN and TP and for each main study factor to be translated (for example, experimental task, (neuroscientific) technique, analysis method). The preliminary framework may improve the translational potential by integration of specific study findings into other preclinical and clinical research fields in TN and TP. Thus, high translational potential of research findings may lead to greater understanding into pathophysiology of mental disorders.



Abbreviations: Ext, extinction; FC, fear conditioning.

Legend.

Animal – Other animal studies in literature

Animal – This animal study

Animal study to run for translation

Animal + Human:

Optional: Translating experimental task from animal to human

Human – This human study

Human study to run for translation

Human – Other human studies in literature

Clinical symptoms/illness

Poster Ref: P3-G-010

Theme: G: Methods and Techniques

The effect of fluid restriction protocols on physiological measures of hydration status in Rhesus Macaques.

Helen Gray[1], Candy Rowe[1], Paul Flecknell[2], Henri Bertrand[2] and Alexander Thiele[1]

[1]Institute of Neuroscience,Newcastle University, [2]Comparative Biology Centre, Newcastle University

Background: Fluid restriction is a widely implemented method for motivating non-human primates (NHPs) in behavioural neuroscience tasks. By restricting the amount of fluid that an individual monkey consumes daily, a researcher can use thirst as a motivator to work during experiments, where correct trials performed by the monkey are rewarded with a droplet of liquid. One primary concern is that researchers risk dehydrating their monkeys, leading to welfare concerns. The aim of this study was to assess the physiological impact of two fluid restriction protocols on primate welfare.

Methods: Four male rhesus macaques were given a period of free access to water, followed by alternating four-week blocks of either a 5-day fluid restriction (followed by 2 days of free water access at the weekend) or 7-day fluid restriction (with no days of free water access). Blood and urine samples were analysed at the end of each block for physiological markers of dehydration (sodium, potassium, calcium, creatinine, urea, and haematocrit in the blood; creatinine, osmolality and specific gravity in the urine). The monkeys' weights were recorded daily.

Results: There were no differences between the two fluid restriction protocols in any physiological measure taken, although some measures were significantly higher when animals were fluid-restricted compared to when they were on free access. None of the physiological measures taken from the blood samples were outside of the normal range established from populations of animals with free water access at all times. Changes in urine composition were indicative of healthy renal function in response to decreased fluid intake.

Conclusion: Under the fluid restriction regimes used, animals kept blood parameters relevant to hydration status within normal healthy ranges.

Poster Ref: P3-G-011

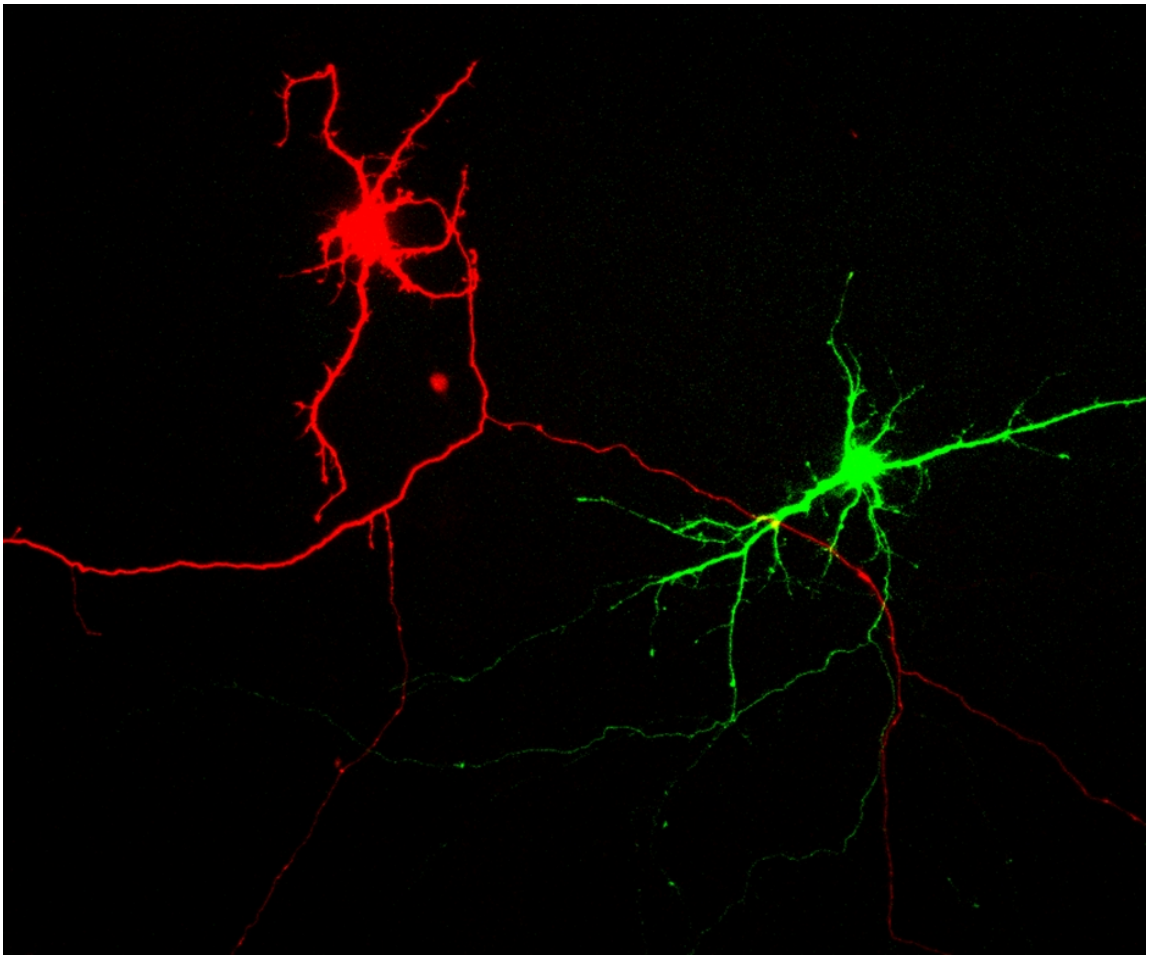
Theme: G: Methods and Techniques

Novel neurophotonics tools for functional studies of neural networks with single cell resolution.

Maciej Antkowiak

University of St Andrews

I will present the current work in my lab which focuses on development and application of novel neurophotonics tools for single cell studies. In particular I will present a technique for laser-mediated rapid delivery of optogenetic genes (*e.g.* Channelrhodopsin) into single selected neurons. A sub-second transfection timescale per cell makes this method more rapid by at least two orders of magnitude when compared to alternative single-cell transfection techniques. We extend the functionality of this technique for wider uptake by neuroscientists by using fast three-dimensional laser beam steering enabling an image-guided ‘‘point-and-transfect’’ user-friendly transfection of selected cells. This novel technology provides the ability to carry out large-scale cell selective genetic studies on neuronal ensembles and perform rapid genetic programming of neural circuits. I will also present my current work towards all-optical electrophysiology of neural networks which will enable high-throughput functional studies on connectivity and plasticity in living neural circuits. This novel experimental approach enables simultaneous purely optical stimulation and readout of activity of hundreds of neurons with single-cell precision, using an all-optical equivalent of patch-clamp electrophysiology.



Two neurons selectively transfected with two different types of plasmid DNA using optical transfection.

Poster Ref: P3-G-012
Theme: G: Methods and Techniques

Counting channels: electrophysiology and super-resolution microscopy.

Matthew Euston, Katarzyna I Cialowicz , Rory R Duncan and Euan R Brown
IB3, Heriot Watt University, Edinburgh

Voltage-gated calcium channels (VGCCs) must lie in close proximity to secretory vesicles at the cell membrane for triggered-exocytosis to occur. It is not known whether this requires a single channel per vesicle, if clusters of channels are involved, and if this relationship differs between cell types. Here we describe our approach to 'counting' channels and determining their distribution using combined electrophysiology and super- resolution imaging with the aim of determining the contribution single channels make to secretion.

Whole-cell voltage clamp was used to determine the number and type of VGCCs in AtT20 cells (by measuring cell capacitance and current density). A novel fluorescently-labelled N-type specific ω-conotoxin was synthesised and its action on N-type channels compared against unlabelled toxin in Chinese Hamster Ovary (CHO) cells transfected with N-type channels. Simultaneous calcium imaging and electrophysiology was carried out with FLUO-4 using Total Internal Reflectance Fluorescence (TIRF) imaging.

Cell capacitance was 14.5 pF, corresponding to a surface area of 1450 μm2. The peak calcium current was -127±15 pA from a -80 mV holding potential. Pharmacology and voltage regimes showed 65%, 11.5% and 23.5% of the current is L-type, N-type and other channel types respectively (n=6). Total VGCC number was estimated to be 13000/cell, meaning there would be an expected 9 VGCCs/ μm2 (if distribution is even). One of these channels would be expected to be N-type. Labelled and unlabelled conotoxin showed 100% block at 3 μM and 0.5μM respectively (n=6). Single-molecule imaging of the labelled toxin showed punctate fluorescence. TIRF calcium imaging showed a random distribution of channels.

Electrophysiology has allowed a model of channel distribution to be created for this cell type. This will be used for informed single-molecule imaging at the membrane with TIRF microscopy. Now we have established this protocol we will use it to examine this relationship in other secretory cell types such as neurons.

Poster Ref: P3-G-013

Theme: G: Methods and Techniques

Assessment of stereotypic behaviours induced by IP injection of apomorphine & strychnine in mice: a novel animal model of Schizophrenia.

Paria Sharafi Badr, Faeghe Baha'addini Beigy and Fateme Pirsalami

Shiraz University of Medical Sciences, Iran

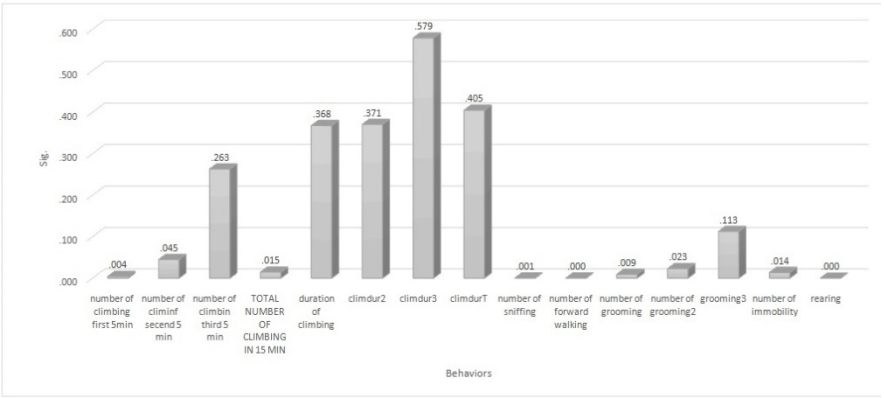
Background: Schizophrenia is one of the chronic and debilitating psychotic mental disorder in more than 1% of population in all over the world. The dopamine hypothesis proposes that a dysfunction in dopamine neurotransmission is the cause of the positive symptoms of the schizophrenia. Also a glutamatergic deficiency such as decreased glutamate release and a loss of GABA neurotransmission activity has been reported in schizophrenic brains. In this study, stereotypic behaviours of mice were assessed using Apomorphine and Strychnine as a dopamine agonist and a GABA antagonist, respectively.

Materials and methods: In this experimental study, 27 male albino mice weighing 25-30g were collected randomly and divided in 3 groups. Strychnine ((0.1 mg)⁄ml) and Apomorhine ((5mg)⁄ml) were injected singly and intraperitoneally(IP). Time out for injections was 15 minutes. As soon as possible stereotypic behaviours such as climbing, grooming and sniffing were recorded. Effects of antipsychotic drugs were assessed.

Results: The results showed that separated injection of Apomprhine and Strychnine, induced stereotypic behaviours such as climbing and grooming ($p<0.05$). Coinjection of Apomorphine (5mg⁄kg) with Strychnine (0.1 mg⁄kg), caused significant increase in climbing and grooming behaviours ($p< 0.05$). Consumption of Haloperidol and Clozapine stopped stereotypic behaviours induced by coinjection of Strychnine and Apomorphine.

Conclusion: Remarkable result of this study is the role of Strychnine as a GABA antagonist on increasing stereotypic behaviours in mice similar to that of Apomorphine. It is not clear if climbing induced by Strychnine may serve as an animal model of psychosis based on the manipulation of GABAergic system.

		N	Mean	Std. Deviation	Std. Error
TOTAL NUMBER OF CLIMBING IN 15 MIN	w+asc(control)	7	5.43	10.114	3.823
	str0.1	7	6.00	7.550	2.854
	str0.1+apo5	10	14.20	9.920	3.137
	apo5	10	5.90	4.795	1.516
	hal0.03+str0.1+apo5	4	.00	.000	.000
	clz2.5+str0.1+apo5	4	.00	.000	.000
	Total	42	6.69	8.541	1.318
number of sniffing	w+asc(control)	7	10.29	9.376	3.544
	str0.1	7	30.29	13.671	5.167
	str0.1+apo5	10	24.70	8.274	2.616
	apo5	10	28.10	10.598	3.351
	hal0.03+str0.1+apo5	4	10.75	9.708	4.854
	clz2.5+str0.1+apo5	4	9.75	7.411	3.705
	Total	42	21.29	12.778	1.972
number of grooming	w+asc(control)	7	.43	.535	.202
	str0.1	7	2.14	1.464	.553
	str0.1+apo5	10	1.10	1.287	.407
	apo5	10	2.00	2.108	.667
	hal0.03+str0.1+apo5	4	6.25	5.679	2.839
	clz2.5+str0.1+apo5	4	3.50	3.873	1.936
	Total	42	2.10	2.783	.429
	Total	42	2.55	2.624	.405
number of immobility	w+asc(control)	7	3.00	1.732	.655
	str0.1	7	4.57	3.552	1.343
	str0.1+apo5	10	1.20	1.398	.442
	apo5	10	1.00	.816	.258
	hal0.03+str0.1+apo5	4	2.50	3.109	1.555
	clz2.5+str0.1+apo5	4	1.75	.957	.479
	Total	42	2.19	2.308	.356



Behaviours and Their Significance ($p<0.05$)

Poster Ref: P3-G-014

Theme: G: Methods and Techniques

Resolving the influence of locus coeruleus on neuronal activity in the prefrontal cortex.

Amisha Patel, Louise Hickey, Emilie Werlen, Matt Jones and Anthony Pickering

Department of Physiology and Pharmacology, University of Bristol

Noradrenergic neurones of the locus coeruleus (LC) provide an extensive input to cortical territories and influence a number of higher-order cognitive functions including: sleep/wake, arousal, perception, memory and attention. Specific projections from the LC to prefrontal cortex (PFC) are believed to play a role in attention and working memory. To examine the influence of the LC on prefrontal cellular activity we have used selective optoactivation in combination with chronic tetrode recordings in rats.

Male rats were anaesthetised for recovery surgery (ketamine 50mg/kg and medetomidine, 300µg/kg). A canine adenovirus type2 vector engineered to express channelrhodopsin2 driven by a catecholaminergic selective promoter (CAV2-PRS-ChR2-mCherry) was stereotaxically injected unilaterally into the LC and a custom made tetrode–optrode microdrive was implanted. The optic fibre was positioned directly above the LC and tetrodes were positioned in the PFC (cingulate and prelimbic territories). Over the next 3 months animals were connected to a recording system (Neuralynx) for cellular recordings and optoactivation (445nm, Omicron laser) - using flexible cables and rotary joints to allow free movement – and placed in their home cage. Extracellular recordings of PFC neurones and local field potentials were recorded from throughout each recording session (2-4 hours) over a 3-month period.

Stable recordings were reliably obtained from assemblies of individually discriminable PFC neurones during LC stimulation. From a baseline sleep state, activation of the LC produced a stereotyped temporally discrete change in cellular activity in the PFC with individual neurones showing consistent excitations or inhibitions across epochs. A similar pattern of activity change was observed across multiple recording sessions. The pattern of PFC response was sensitive to sleep-wake state. These findings demonstrate the feasibility of long-term optoactivation of the LC in combination with tetrode recordings over a period of months and indicate that the approach can be used to examine the influence of the noradrenergic projection on populations of prefrontal cortical neurones.

Conflict of interest declarations

Poster number P1-C-027
Timo Giesbrecht and Anna Thomas are employees of Unilever Research and Development, who part-funded the research.

Poster number P1-D-018
Thomas Blackmore, Conor Eastop, Keith Phillips and Francois Gastambide are employees of Eli Lilly & Co. Ltd.

Poster number P1-D-021
There are no commercial interests, however ZingUp are a partner with the University of Sheffield under an EU Horizon 2020 proposal currently under review.

Poster number P1-D-054
The study was funded by the Wellcome Trust Fellowship grant for VV (093705/Z/10/Z) and Cambridge NIHR Biomedical Research Centre. VV and NAH are Wellcome Trust (WT) intermediate Clinical Fellows. LSM is in receipt of an MRC studentship. The BCNI is supported by a WT and MRC grant. MF is funded by NIMH and NSF grants and is consultant for Hoffman LaRoche pharmaceuticals. The remaining authors declare no competing financial interests.

Poster number P1-D-058
JN has received expenses to attend conferences and fees for lecturing and consultancy work (including attending advisory boards) from the manufacturers of various neuropsychiatric drugs.

Poster number P1-F-005
Joanna Neill has received expenses to attend conferences and fees for lecturing and consultancy work (including attending advisory boards) from the manufacturers of various antipsychotic drugs.

Poster number P1-F-021
Dr Sahakian reported receiving consulting and lecture fees from Lundbeck, consulting fees from Cambridge Cognition, and grants from Janssen/J&J. Dr Robbins reported receiving consulting fees from Cambridge Cognition, Lilly, Merck, Lundbeck, GSK, Teva and Shire, grants from GSK, Lilly and Lundbeck, and payments from Cambridge Cognition for 'CANTAB', and honorarium from Springer-Verlag for editorial duties for 'Psychopharmacology'.

Poster number P1-F-050
WRM has participated in Illumina sponsored meetings and received travel reimbursement and an honorarium for presenting at these events.

Poster number P1-G-004
This project is funded by a BBSRC CASE studentship in partnership with Reinnervate Ltd.

Poster number P2-D-016
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Poster number P2-D-061
Paid employees of Eli Lilly & Co. Ltd.

Poster number P2-E-002
All authors are employees of Lilly.

Poster number P2-E-004
We were all Eli Lilly emplyees at time of preparation.

Poster number P2-F-020
The present research has been partly funded by Nutricia Research. Martine Groenendijk, John W. Sijben, and Martijn C. de Wilde are employees of Nutricia Research.

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Dr Large and Alvaro are employees of Autifony Therapeutics who synthesized the compound tested.

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Poster number P3-B-032
A.M.T. is an inventor of the microfluidic chambers (US 7419822 B2) and has financial interest in Xona Microfluidics, LLC. R.B., M.N., R.D., and J.K. declare no competing financial interests.

Poster number P3-C-025
The authors LL, JP, KN and JR, and the University of Washington have intellectual property associated with the technology described in this abstract.

Poster number P3-E-008
Authors AM and JL work for the company, Sable Systems, that produces the 'Promethion' instrument line that made this measurments possible.

Poster number P3-E-013
Dr Keith Wafford and Dr Mathieu Nollet are employed by Eli Lilly and Company.

Poster number P3-F-020
M.M. and M.N.P are AstraZeneca employees.

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ST has received research project funding from Lundbeck & Merck Serono. KM has Chaired advisory boards for studies of Deep Brain Stimulation for Obsessive-Compulsive Disorder sponsored by Medtronic. He has received educational grants from Cyberonics Inc. & Schering Plough, and he has received research project funding from Lundbeck, Merck Serono & Reckitt Benckiser and also from St Jude Medical for a multi-centre clinical trial of Deep Brain Stimulation for depression. He has received travel and accommodation support to attend meetings from Medtronic and St Jude Medical. JDS has received research funding via an honorarium associated with a lecture from Wyeth. All other authors report no biomedical financial interests or potential conflicts of interest.

Poster number P3-F-040
A.M.T. is an inventor of the microfluidic chambers (US 7419822 B2) and has financial interest in Xona Microfluidics, LLC. T.N., R.B., R.L., and B.D.P. declare no competing financial interests.

Poster number P3-F-041
ALM and NKP have presented at Medtronic sponsored conferences. The Friends of Frenchay Hospital and Medtronic contributed with donations.

Poster number P3-F-042
David Nutt is an advisor to British National Formulary, MRC, GMC, Dept of Health, is President of the European Brain Council, past President of the British Neuroscience Association and European College of Neuropsychopharmacology, chair of the Independent Scientific Committee on Drugs [UK], is a member of the International Centre for Science in Drug Policy, advisor to Swedish government on drug, alcohol and tobacco research, editor of the Journal of Psychopharmacology, sits on advisory Boards at Lundbeck, MSD, Nalpharm, Orexigen, Shire, has received speaking honoraria (in addition to above) from BMS/Otsuka, GSK, Lilly, Janssen, Servier, is a member of the Lundbeck International Neuroscience Foundation, has received grants or clinical trial payments from P1vital, MRC, NHS, Lundbeck, has share options with P1vital, has been expert witness in a number of legal cases relating to psychotropic drugs, and has edited/written 27 books - some purchased by pharma companies.

Trevor Robbins has research grants with Eli Lilly and Lundbeck, has received royalties from Cambridge Cognition (CANTAB), has received editorial honoraria from Springer Verlag, Elsevier, Society for Neuroscience; has performed educational lectures for Merck, Sharpe and Dohme and does consultancy work for Cambridge Cognition, Eli Lilly, Lundbeck, Teva and Shire Pharmaceuticals.

Anne Lingford-Hughes has received honoraria from Lundbeck and research support from GSK for a PhD studentship.

All other authors declared no conflict of interest

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Henstridge, Chris	P2-D-019	Johnstone, Nicola	P2-C-009
Herman, Aleksandra	P1-F-032	Jones, Glynn	P2-G-009
Hernández-Rabaza, Vicente	P3-D-022	Jones, Lauren	P3-F-018
Herranz-Martin, Saul	P3-F-027	Jørgensen, Henriette S.	P2-C-014
Herrgen, Leah	P2-A-003	Jozefowiez, Jeremie	P3-D-033
Herrmann, Abigail	P3-B-017	Kaelen, Mendel	P3-D-039
Hird, Emily	P1-D-040	Kalafatakis, Konstantinos	P2-D-004
Hislop, James	P2-F-009	Kalyanapu, Swetha	P1-B-016
Hobson, Hannah	P3-G-003	Karyka, Evangelia	P3-F-025
Honda, Takato	P1-D-051	Kathe, Claudia	P1-F-048
Hope, Anthony	P2-F-049	Katona, Linda	P2-B-008
Hope, Jilly	P1-F-007	Kaufmann, Timothy J	P3-F-029
Horak, Martin	P3-B-020	Kavlie, Ryan G	P3-C-024
Hornsby, Amanda	P2-D-058	Kealy, John	P1-D-022

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Keemink, Sander	P2-C-010	Leung, Yuk	P1-F-025
Khalighinejad, Nima	P3-C-015	Li, Ziwen	P1-A-004
Khan, Muhammad Umair	P3-F-005	Lichnerova, Katarina	P1-B-028
Khan, Muhammad Umair	P3-F-003	Lim, Sol	P1-A-017
Khan, Muhammad Umair	P3-F-002	Lima, João	P1-D-056
Kidd, Kirsty	P2-C-005	Little, Rosie	P2-A-015
Kidd, Kirsty	P2-C-008	Liu, Wenhua	P1-D-009
Kijewska, Wioleta	P2-D-036	Llavero Hurtado, Maica	P3-B-003
Kim, Sung Hwa	P2-D-003	Lohse, Michael	P3-D-034
King, Declan	P1-B-001	Longo, Matthew	P1-C-031
King, S.	P1-F-008	Loomis, Sally	P2-E-004
Kinnavane, Lisa	P1-D-037	Lopez-Huerta, Violeta	P1-B-005
Kirby, Melissa	P3-D-027	Loss, Omar	P1-B-007
Kireev, Maksim	P2-D-042	Lowe, Michael	P2-F-002
Kirk, Gregory	P1-G-014	Lowe, Scott	P2-C-029
Kleteckova, Lenka	P2-F-042	Lyngholm, Daniel	P2-A-005
Kocagoncu, Ece	P1-D-034	Lyon, Stephanie	P1-D-059
Koromina, Maria	P1-F-009	Lyons, David J	P3-E-010
Kosilo, Maciej	P3-A-019	Lyons, Georgina	P3-G-004
Koss, David	P2-F-037	Mahapatra, Chitaranjan	P2-B-003
Koziakova, Mariia	P1-F-036	Maia, Susana	P1-D-043
Kraev, Igor	P2-B-017	Maierbrugger, Katja T.	P2-A-011
Krausova, Barbora	P3-B-011	Makhtar, Siti Noormiza	P2-G-011
Kreilkamp, Barbara	P2-A-016	Malalasekera, Nishantha	P1-D-029
Kritikos, Minos	P3-B-026	Malavasi, Elise	P1-B-017
Kuipers, Jan Rouke	P2-D-047	Malekizadeh, Yasaman	P1-B-004
Kuznetsova, Ksenia	P3-D-058	Malizia, Andrea L	P3-F-041
L.Tremoleda, Jordi	P1-G-013	Mallah, Shahida	P2-B-043
Ladouce, Simon	P3-D-010	Manca, Maurizio	P1-B-025
Landgraf, Matthias	P3-B-039	Mandane, Baguiasri	P1-A-001
Langfelder, Antonia	P3-C-023	Mandane, Baguiasri	P1-F-001
Langston, Rosamund	P1-D-061	Maneesh, Kuruvilla	P2-D-007
Lautarescu, Alexandra	P3-F-011	Manktelow, A.E.	P1-D-038
Lax, Nichola	P2-F-046	Manning, Katherine	P1-F-022
Lazutkaite, Greta	P3-B-037	Manuel, Martine N	P2-A-001
Leather, Thomas	P1-A-013	Maqbool, Ayesha	P1-F-002
Lee, Eugene L.Q.	P3-E-016	Márkus, Nóra	P2-B-034
Lee, Graham	P3-F-045	Marsh, Jade	P3-F-013
Lee, Graham	P3-A-014	Marshall, Hayley	P1-D-044
Lee, Yeseul	P2-D-026	Martelletti, Elisa	P2-C-011
Lee, Ying	P3-D-036	Martinez de Morentin, Pablo B.	P2-E-013
Leger, Marianne	P1-F-005	Martinez-Gonzalez, Cristina	P3-C-022
Lempriere, Sarah	P3-B-035	Mason, Robert	P1-G-005
Leung, Wai Hin	P1-F-017	Mastroberardino, Serena	P2-D-045

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Masuda-Nakagawa, Liria M	P3-C-016	Mulholland, Carl	P1-F-010
Mateos-García, A	P1-D-045	Murphy, Laura C.	P3-B-009
Mattschey, Jennifer	P3-C-012	Murphy, Lita	P2-F-031
Maysami, Samaneh	P2-F-026	Murphy, Nicholas	P1-G-009
McCartney, Daniel	P1-F-050	Murray, Christina	P3-F-001
McFarquhar, Martyn	P2-G-004	Muzzu, Tomaso	P2-C-013
McGregor, Gemma	P1-B-043	Mysiak, Karolina S.	P2-A-006
McKillop, Laura E.	P2-E-003	Naghynajadfard, Maryam	P3-F-007
McNamara, Colin	P1-D-057	Navarro-Francés, CI	P1-D-041
McNamee, Jennifer	P2-F-051	Neira, Lara	P3-D-049
McNeil, Chris	P2-D-031	Nelson, Andrew	P1-D-012
Megaw, Roly	P1-B-023	Nelson, Lucy	P1-F-024
Mehdar, Khlood	P3-F-028	Nelvagal, Hemanth Ramesh	P3-F-032
Melis, Valeria	P1-F-037	Newson, Margaret	P3-D-041
Mensch, Sigrid	P2-B-025	Ng, Sher May	P1-F-058
Merricks, Edward	P3-F-044	Nicodemus, Kristin	P3-A-009
Merrison-Hort, Robert	P3-C-021	Nollet, Mathieu	P3-E-013
Michel, Christophe	P1-B-018	Nonaka, Mio	P1-D-005
Mifsud, Karen R.	P3-E-009	Nonaka, Mio	P1-D-004
Mikheenko, Yevheniia	P1-D-046	North, Katherine	P1-A-012
Milczarek, Michal	P2-D-013	O'Connor, Angela May	P1-C-001
Miller, Jessica	P3-D-005	O'Connor, Angela May	P3-A-021
Mills, Jennifer	P3-D-020	Oghenetega, Umukoro	P2-B-011
Miron, Veronique E	P2-F-024	Okunoren-Oyekenu, Yewande	P2-A-009
Mirzaei, Nazanin	P3-F-055	Olenik, Mark	P2-C-015
Mistry, Sumit	P1-D-010	Olt, Jennifer	P1-C-013
Mitchell, Anna	P2-D-002	Oostland, Marlies	P1-C-029
Mitchell, Simon	P2-D-043	Openshaw, Rebecca	P1-F-020
Mole, Jilu	P2-C-012	O'Reilly, Jamie	P1-F-052
Mole, Tom	P2-D-006	O'Sullivan, Niamh	P2-F-011
Mölich, Andreas	P3-E-008	O'Sullivan, Niamh	P2-F-010
Montagud-Romero, Sandra	P1-D-049	Owens, Rosie	P3-B-001
Moore, Emma	P2-C-028	Pallier, Patrick N.	P2-F-052
Morcom, Alexa M.	P3-A-018	Pallier, Patrick N.	P2-F-020
Morcom, Alexa M.	P1-D-036	Papasavvas, Christoforos	P1-F-051
Morè, Lorenzo	P1-B-019	Papoutsi, Marina	P2-C-022
Moreau, Pierre-Henri	P1-F-038	Paracchini, Silvia	P1-A-015
Moreno, Andrea	P1-D-001	Parish, Elisa	P2-A-007
Morris, Laurel	P1-D-054	Parkinson, Jim	P3-D-023
Morton, Andrew	P1-A-016	Parrish, Robert	P3-F-034
Moss, Jonathan	P3-B-025	Parrish, Robert	P3-F-033
Moudio, Serge	P3-B-010	Patel, Amisha	P3-G-014
Moungou, Athanasia	P1-C-023	Payne, Heather	P3-A-017
Muhlert, Nils	P1-D-030	Payne, Thomas W	P2-B-023

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Pearson, Craig	P3-B-041	Rentesi, Georgia	P2-F-013
Pei, Yue	P3-F-022	Ridler, Thomas	P1-F-014
Pennifold, Jane	P1-B-014	Riley, Timothy	P1-C-012
Pennington, Catherine	P1-D-026	Ritchie, Louise	P1-B-029
Perentos, Nicholas	P3-E-015	Robbins, Jacqueline	P3-F-020
Perry, Gavin	P1-C-020	Roberts, Sheridan	P1-B-011
Persson, Bjorn	P2-D-009	Robertson, Barbara-Anne	P2-D-022
Pessoa, Veridiana	P1-F-026	Robertson, Graham	P1-G-012
Petitet, Pierre	P3-D-008	Robertson, Jonathan, M	P3-F-043
Petitto, Evelina	P1-B-008	Robson, Emma	P3-B-005
Pezze, Marie	P1-D-032	Rolls, Edmund	P2-C-007
Phillips, James	P3-C-025	Rolls, Edmund	P1-C-005
Phillips, Jonathan	P2-G-012	Rolls, Edmund	P2-D-025
Phillips, Jonathan	P2-F-005	Roseman, Leor	P3-C-005
Phillips, Thomas	P3-A-015	Rosewell, Natalie	P2-F-028
Pickett, Eleanor	P2-B-041	Rossato, Janine I	P1-D-003
Pickford, Jasmine	P2-B-028	Rothärmel, Roman	P2-B-032
Picton, Laurence	P2-C-027	Roy, Marcia	P2-B-029
Piggot, Judith	P3-A-010	Rzechorzek, Nina	P1-B-034
Pirmoradian, Sahar	P2-G-010	Sabec, Marie	P3-D-002
Pistikova, Adela	P3-D-003	Sabry, Moustafa	P3-A-006
Plucinska, Kaja	P2-F-022	Saffrey, M.Jill	P1-H-006
Powell, Anna	P1-A-011	Salih, Shelanah	P3-F-015
Privitera, Lucia	P1-B-038	Salih, Shelanah	P1-F-040
Pruski, Michal	P3-A-003	Samu, David	P2-D-012
Pulix, Michela	P1-F-041	Sanderson, Thomas M.	P1-B-041
Purali, Nuhan	P3-B-019	Sandu, Anca-Larisa	P2-D-028
Qiu, Jing	P2-B-015	Santoro, Matteo	P2-F-035
Qiu, Zhen	P2-G-001	Savage, Michael	P3-C-010
Rabiaa, Entedhar Kadhum Huss	P1-A-003	Scharf, Robert	P1-G-008
Rae, Charlotte	P1-F-021	Schiemann, Julia	P1-C-004
Raginis-Zborowska, Alicja	P3-F-016	Schröter, Manuel	P3-A-016
Rajani, Rikesh	P3-F-021	Schuhmacher, Laura-Nadine	P3-C-004
Ramachandran, Sanjeev	P1-G-015	Scoberg-Evans, Jordan	P3-F-019
Rammos, Alexandros	P3-D-042	Seaton, Gillian	P3-B-006
Randall, Andrew	P2-B-010	Seel, Sabrina	P1-D-042
Ratcliff, Michael	P2-F-054	Seiss, Ellen	P3-D-026
Raval, Pooja	P2-B-031	Sevenster, Dieuwke	P1-D-055
Reader, Arran	P1-C-007	Shaffick-Rrichardson, Keir	P2-F-034
Rebollar, Monica	P3-D-044	Shah, Darshna	P3-B-018
Rees, Daniel	P2-F-056	Shanks, Elaine	P2-E-002
Reeve, Amy	P2-A-013	Sharafi Badr, Paria	P3-G-013
Regan, Philip	P3-B-027	Sherman, Maxine T.	P2-C-030
Renault, Kathleen	P2-B-033	Sherwood, Mark	P2-B-006

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Shoaib, Mohammed	P3-F-035	Thompson, Karen	P2-B-038
Simon, Anna	P1-B-039	Thouin, Anais	P2-F-027
Sims, Robert	P2-B-024	Threlfell, Sarah	P1-G-010
Sindi, Abdulmajeed	P2-A-010	Tigaret, Cezar M.	P1-B-037
Sivakumaran, Magali	P2-D-008	Tilston-Lunel, Andrew	P3-B-008
Smith, Anna	P3-D-025	Tolomeo, Serenella	P3-F-049
Smith, Jackson E. T.	P2-G-008	Tong, Godwin	P2-A-019
Smithers, Hannah	P2-F-016	Topiwala, Anya	P3-D-006
Solanka, Lukas	P2-D-046	Topping, Matthew P	P3-C-011
Spray, Amy	P3-D-013	Tossell, Kyoko	P3-B-024
Stankevicius, Aistis	P3-F-050	Treiber, Christoph	P2-B-039
Stein, Alwina	P2-F-004	Trew, Fiona	P2-F-003
Steinberg, Eleonora	P3-E-011	Trotter, Paula	P2-C-004
Sterratt, David	P3-A-012	Tsujimura, Hikaru	P3-D-050
Stevenson, Carl	P1-D-035	Tsunematsu, Tomomi	P1-G-001
Stolicyn, Aleks	P3-F-024	Turunc Bayrakdar, Sinem Ezgi	P3-F-036
Stoney, Patrick	P3-E-001	Tweedy, Clare	P3-B-014
Storchi, Riccardo	P1-C-011	Udakis, Matt	P2-D-010
Straub, Volko	P3-A-008	Unal, Gunes	P2-D-017
Stringer, Michael S	P2-F-045	Vaghi, Matilde M.S.	P3-D-051
Stubbendorff, Christine	P1-D-053	Valencia-Torres, Lourdes	P2-E-007
Suri, Sana	P1-D-020	Valton, Vincent	P2-D-021
Surmeli, Gulsen	P3-D-035	van de Lagemaat, Louie	P3-D-014
Susilaradeya, Damar	P1-C-018	van der Heide, Susan	P3-G-006
Sverrisdottir, Yrsa Bergmann	P1-H-004	Vandrey, Brianna	P2-D-035
Sweeney, Yann	P2-D-032	Varughese Chacko, Lijo	P2-G-006
Swire, Matthew	P2-B-021	Vatansever, Deniz	P3-D-019
Sykes, Lucy	P2-D-014	Vaughan, Frances	P3-E-002
Tabassum, Nazool-e	P3-D-028	Velasco, Maria	P2-B-014
Taheri, Amy	P3-B-033	Vincent, Clementine	P1-B-042
Takeuchi, Tomonori	P1-D-007	Vithanage, Nethmi	P3-D-001
Tam, Sze Wah	P3-F-012	Vousden, George	P3-D-048
Tamagnini, Francesco	P2-F-036	Wade, Cian	P1-C-006
Tardieu, Camille H	P3-C-019	Wallace, Victoria	P1-C-022
Tateyama, Kei	P2-F-047	Wallis, Stephanie	P2-F-053
Taylor, Anne	P3-B-032	Walmsley, Lauren	P2-E-012
Taylor, Anne	P3-F-040	Walmsley, Lauren	P2-E-014
Taylor, Peter	P1-F-006	Walpert, Madeleine	P1-G-011
Teles-Grilo Ruivo, Leonor Maria	P1-B-026	Walsh, Darren	P3-B-004
Tennant, Sarah	P2-D-048	Wang, Yujiang	P1-A-005
Tezuka, Taro	P3-G-008	Watanabe, Sakurako	P1-B-015
Thakrar, Chiraag	P3-A-002	Watson, David	P1-F-033
Thau-Zuchman, Orli	P1-F-018	Watson, Thomas	P2-D-033
Theil, Thomas	P2-A-018	Werlen, Emilie	P2-D-055

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West, Steven J.	P2-G-013
Westacott, Laura	P2-B-040
Wheeler, Annamarie	P2-D-054
White, Samantha	P2-F-044
Whitehead, Garry	P2-B-020
Wickens, Robin	P2-F-048
Wicklein, Martina	P2-C-001
Willems, Roland	P3-F-046
Wilson, Emma	P3-C-014
Winlove, Crawford	P1-F-044
Winlove, Crawford	P1-F-046
Winlove, Crawford	P1-F-043
Winlove, Crawford	P1-F-045
Woloszynowska-Fraser, Marta	P1-D-028
Wong-Lin, KongFatt	P2-C-026
Wong-Lin, KongFatt	P2-E-005
Wong-Lin, KongFatt	P2-G-014
Wood, Bryony	P2-D-040
Wood, Shona	P3-E-007
Wright, Hazel	P1-H-001
Wright, Michael	P1-D-062
Wright, Vicki	P2-D-023
Wu, Chi-Hsu	P2-C-006
Wu, Yixing	P1-B-003
Wynne, Paul.J	P1-D-025
Yang, Yujie	P1-A-018
Yavas, Ersin	P2-F-014
Zeng, Yanni	P1-F-027
Zhao, Chen	P2-F-025
Zhu, Fei	P3-B-015
Zinnamon, Fhatarah A.	P2-F-032