Issue No. 88
Spring 2020

BNA Bulletin

THE VOICE OF BRITISH NEUROSCIENCE TODAY

Curious for answers

The neurobiology of curiosity

Painful truths

The genetics of pain

PLUS:

Neuropixels

Neurofeedback for pain

FENS 2020

BNA
British Neuroscience Association

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11-15 July 2020 | Glasgow, UK

Organised by the Federation of European Neuroscience Societies (FENS)
Hosted by the British Neuroscience Association (BNA)

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FENS Federation of European Neuroscience Societies
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John Tenniel's illustration from *The Nursery 'Alice'* (1889), a shortened version of *Alice's Adventures in Wonderland* adapted by Lewis Carroll for young children. Curiosity was too much for young Alice. See page 30 for more on the neuroscience of curiosity. Image: WikiMedia Commons.

BNA Bulletin
Editor:
Ian Jones, Jinja Publishing Ltd
Design and production:
Jag Matharu,
Thin Air Productions Ltd

Advertising in the BNA Bulletin: Contact the BNA office (office@bna.org.uk) for advertising rates and submission criteria.

ISSN: 1475-8679

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BNA Council and National Committee

New treatments for pain

Thursday 14th May 2020 at Erl Wood, Surrey
FREE for BNA members!

www.bna.org.uk

'New treatments for pain' will bring together people from the commercial, academic, and not-for-profit sectors to share current knowledge, identify future directions, and enable collaboration, providing delegates with meaningful and practical ways to accelerate their own work.

This event will incorporate presentations, networking and discussion sessions to share knowledge and increase collaboration in pain research and bring together people from the commercial, academic, and not-for-profit sectors to share current knowledge, identify future directions, and enable collaboration, providing delegates with meaningful and practical ways to accelerate their own work.

The day will start with an insight into the lived experience of pain, via a conversation between a pain clinician and their patient. This will lead into a session reflecting back at how pain treatments have developed and then bringing us right up to date with the current situation in drug development and research.

We will go on to enjoy a smorgasbord of rapid-fire talks giving a taste of exciting research from around the UK and in different sectors. For instance, what do we know about dementia and pain, autoimmunity, biomarkers and big data?

A key component of the meeting will be the opportunity to dig deeper into areas of individual interest, via facilitated small group discussions. This will allow delegates to direct the focus into areas as they wish. Group discussions will be captured during the meeting and key outcomes shared.

The programme is being led by a team of industry and academic experts who will also be leading brainstorming breakout sessions on the day, including:

Craig Bullock - Versus Arthritis
Anne Cooke - BNA
Jenny Laird - Eli Lilly
Emanuele Sher - Eli Lily

Lunch and refreshments will be provided, and there will be networking opportunities

BNA British Neuroscience Association

Lilly

VERSUS ARTHRITIS

Message from the President and Chief Executive

Dear BNA Members

We've had an incredible winter, despite the record rainfall! One of the highlights was the launch of our high-profile campaign, 'Credibility in Neuroscience', with an event at the House of Commons in late November. In front of a broad guest list of politicians, media, academics and members, we unveiled our manifesto – with the aim to raise awareness and enable all neuroscientists to stay informed about credibility. You can keep up to date with all things 'InCredible' at **www.bnacredibility.org.uk**.

We've also been working hard on advocacy. A recent example has been our contribution, via our Trustee for Research Policy, Narender Ramnani, to a POSTnote on brain–computer interfaces, focusing on the underpinning technology, its applications, and the associated ethical and regulatory challenges.

Of course, central to our campaigning work is making sure we properly represent your voice, as members. That's why it's always a treat to speak to so many of you at our annual Christmas Symposium. The latest symposium, on pain, was a particular success. Held at iconic Bush House at King's College London, the meeting included speakers from institutions across the UK and Europe, and featured on Radio 4's *All in the Mind*.

Looking forward, we're currently in full throttle as host society for FENS 2020 (11–15 July). We're proud to be helping to host 'introductory courses' on 10 July 2020. These accessible introductions, delivered by internationally renowned researchers, will increase your knowledge and perhaps even stimulate a change in career direction. Plus, we're also helping to stage a city-wide 'Great Glasgow Brain Fest' for the wider public. Don't forget, as members you benefit from discounted registration rates.

Another date for your diary: 14 May 2020. At Eli Lilly's Research Centre in Surrey, we'll be hosting 'New treatments for pain', a meeting bringing together the commercial, academic, and not-for-profit sectors. The aim is to share current knowledge, identify future directions, and enable collaboration, providing delegates with practical ways to accelerate their own work. See our website for full details.

As you can see, there's a lot going on! Our members remain at the heart of our work, so do get in touch if there's anything we can help you with. It's only by strengthening and growing our very special, collaborative and innovative neuroscience community that we can continue to advance neuroscience in the UK and beyond.

Annette Dolphin
President

Anne Cooke
Chief Executive

Manifesto launch

The BNA launched its 'Credibility in Neuroscience' manifesto at an evening reception at the House of Commons on 25 November 2019, with guest speakers including BNA Patron **Lord Winston** and **Dorothy Bishop** (Oxford) as well as BNA Chief Executive **Anne Cooke**.

The vision of our manifesto is for neuroscience research to be as robust, reliable, replicable and reproducible as possible. It is backed by three commitments: to support a shift in research culture that is welcomed and desired by the whole neuroscience research community; to equip all neuroscientists with the skills, knowledge, tools and processes they need to carry out credible neuroscientific research; and to change the landscape in which neuroscientists operate so that the influences that drive neuroscience research also drive the most credible research.

Thanks to generous funding from the Gatsby Charitable Foundation, we are developing a significant programme of activities, promoting and supporting credibility in neuroscience research over the next ten years. Further information about our manifesto, planned activities and credibility more generally can be found on our dedicated new website (**www.bnacredibility.org.uk**).

Today in Parliament

In October 2019, the BNA was accepted as a member of the Parliamentary and Scientific Committee (P&SC). Established in 1939, this committee is a key interface between scientists and parliamentarians, and will provide valuable opportunities for the BNA to inform discussion and decision-making in both the House of Commons and the House of Lords on issues related to neuroscience. The BNA will be represented on the P&SC by **Narender Ramnani**, Trustee for Research Policy.

Never the twain

In November 2019, the BNA and the Sainsbury–Wellcome Centre at UCL teamed up to organise a lunchtime event on the implications of the Research Excellence Framework (REF) for reproducibility. 'Never the twain shall meet' featured presentations from open science advocate **Marcus Munafo** (Bristol), BNA President-Elect **Rik Henson** (Cambridge) and **Helena Mills**, Head of REF Policy at Research England.

Neuro Nets

In October 2019, the BNA took part in one of the first regional neuroscience update days – 'Neuro Nets' – in Bristol. The events are being run across the UK as part of the Royal College of Psychiatrists' Integrating Neuroscience Project, supported by the Gatsby Charitable Foundation and Wellcome, which aims to bridge the gap between clinical psychiatry and neuroscience. Bristol delegates had the opportunity to hear about the latest ground-breaking research and its implications for understanding and treating psychiatric conditions, as well as to network with scientific and clinical colleagues. See **bit.ly/2H1Y2LC** for more details of the Integrating Neuroscience Project.

Brain teasers

BNA associate members can now take advantage of an enhanced version of the 'Ask a Scientist' service. Associate members can submit queries to the BNA office, which identifies a suitable expert able to answer it. As well as responses being sent to the original questioner, they will now also be included in the e-bulletin sent to all associate members, along with the name of the scientist who answered the question and any other relevant further information.

This initiative is a key part of our commitment to enabling greater sharing of information and growing the connection between associate members and scientists. If you have a question you would like answered, send it to **office@bna.org.uk**.

Brain Fest

As well as a rich menu of scientific goodies, the BNA's Host Society Committee is planning a full programme of public events – under the banner of the 'Great Glasgow Brain Fest'. The main event will be held on the weekend before FENS, 4–5 July, at Glasgow Science Centre. Full details of the programme will be announced later in the spring.

Local News and Events

Sheffield success

Congratulations to the Sheffield Institute for Translational Neuroscience (SITraN), which has been awarded the Queen's Anniversary Prize for innovation in neuroscience. The prize recognises outstanding work by UK higher education institutions demonstrating quality and innovation in their research, and this award reflects Sheffield's great success in research designed to improve care of people with neurodegenerative conditions such as Parkinson's disease and motor neuron disease. SITraN, which celebrates its 10th anniversary in 2020, is part of the University of Sheffield's newly launched Neuroscience Institute.

UCLAN research day

The University of Central Lancashire (UCLAN) Research Centre for Brain and Behaviour held its first research day in December 2019. The Centre was founded in August 2019 and has been supporting neuroscience research by awarding small research grants, organising monthly seminars by external speakers and holding research days. More information about the Centre can be found at **bit.ly/2S57mV4**.

UCL Neuro Day

The 11th UCL Neuroscience Symposium will be held at the ULC Institute of Education on 26 June 2020. As well as presentations from across UCL, keynote addresses will be delivered by **Vanessa Ruta** (Rockefeller University, New York) and **Philip McGuire** (KCL).

CNS2020

The 2020 Cambridge Neuroscience Seminar (CNS2020) will take place on 15 April 2020. The meeting, to be held at Robinson College, will feature speakers from across the many departments in Cambridge involved in neuroscience research as well as external speakers.

Oxford outreach

Neuroscience researchers across Oxford made major contributions to the IF Oxford Science and Ideas Festival in October 2019. Events included a demonstration of advanced imaging and use of virtual reality in research.

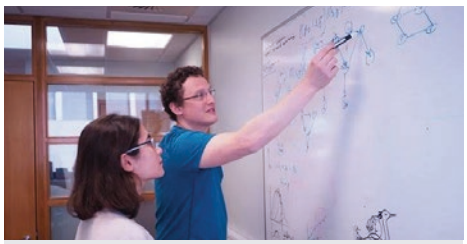
Brain Bee

Cardiff's Neuroscience and Mental Health Research Institute hosted the annual Wales Brain Bee competition in December 2019. Sixth-form science students from six schools came together to compete and test their knowledge of neuroscience in lab challenges, written exam questions and a team neuro-challenge. Three female students from Cathedral School took home first, second and third prizes, and Cathedral School claimed the Wales Brain Bee shield for the second year running.

Edinburgh neuro-day

The 2020 Edinburgh Neuroscience Day took place on 11 March 2020. The Annual Distinguished Lecture 2020 was delivered by **Robin Ali** (UCL).

Blavatnik award



Tim Behrens.

Tim Behrens (Oxford) has received a Blavatnik Award for Young Scientists, selected by the Blavatnik Family Foundation and the New York Academy of Sciences. The awards are the largest unrestricted cash prizes available to scientists under the age of 42. Professor Behrens receives a laureateship worth £75,000 in the life sciences category. The 2020 laureates and finalists were honoured at a ceremony in London on 4 March 2020 and presented their research at a public symposium the following day.

SfN appointee

Jane Haley (Edinburgh) has been appointed to the Society for Neuroscience's (SfN's) Neuroscience Training Committee. Dr Haley is the only non-US member of the 16-strong committee, which oversees the implementation of SfN's higher education and training strategy. Her three-year term began at the 2019 SfN annual meeting in Chicago.

Nature award

Tom Baden (Sussex) is the inaugural winner of the Nature Research Awards for Driving Global Impact. Established in partnership with Tencent, the Awards recognise early-career researchers whose work has made, or has the potential to make, a positive impact on society. As well as his groundbreaking research on vision (see *BNA Bulletin* 81, Autumn 2017), Professor Baden has also been involved in initiatives to use tools such as 3D printing to produce affordable lab equipment.

BPS award

Francesca Happé (KCL) has been awarded the British Psychological Society's (BPS's) Presidents' Award for 2019. Professor Happé has made major contributions to the understanding of the neurocognitive basis of social impairments in autism. The 2019 BPS Lifetime Achievement Award went to **Susan Michie** (UCL).

Mental health

Elaine Fox (Oxford) has been appointed the national Mental Health Impact and Engagement Coordinator by UK Research and Innovation, the umbrella body of the UK Research Councils. She will play a key role in promoting the coordination of collaborative and multidisciplinary research in mental health.

RCPE award

Sarah Tabrizi (UCL) has been awarded the Alexander Morison Medal by the Royal College of Physicians of Edinburgh (RCPE). Her co-head of department, **Nick Fox**, received the same recognition the previous year. Professor Tabrizi has made landmark contributions to the understanding and treatment of Huntington's disease.

Graham Bull Prize

Sarosh Irani (Oxford) has been awarded the Royal College of Physicians' Graham Bull Prize in Clinical Science/Goulstonian Lectureship for his work in autoimmune neurology.

Synaptome funding

Seth Grant (Edinburgh) has been awarded £1.3m by Wellcome to continue his work mapping the molecular composition of the synapse across the brain.

Edinburgh award

Charles ffrench-Constant received Edinburgh's 2019 Chancellor's Award for Research Excellence. Reflecting the great strength of Edinburgh neuroscience, the previous year's Chancellor's Award went to **Richard Morris**.

Gontijo Award

Laura Ferraiuolo (Sheffield) was the winner of the 2019 Paulo Gontijo Award, in recognition of her work on glial cells and motor neuron disease. Established in 2007, the Paulo Gontijo Award recognises early-career researchers working on the causes and treatments of motor neuron disease.

Epilepsy award

Angela Vincent (Oxford) received the Research Recognition Award, Clinical Science, at the 2019 annual meeting of the American Epilepsy Society. Professor Vincent, who shared the award with J Dalmau, has made major contributions to epilepsy research and treatment, and was the BNA Outstanding Contribution to Neuroscience award winner in 2015.

Angela Vincent.

Mike Berridge

The BNA was saddened to hear of the death of Sir Michael Berridge FRS in February 2019. Professor Berridge carried out pioneering research on signal transduction, particularly on inositol trisphosphate signalling and its links to intracellular calcium release.

News in Brief

Chicken stress

Tom Smulders (Newcastle) is leading a €3.9m European initiative, funded by the EU Marie Curie Fund, exploring how stress affects the chicken brain. The ChickenStress European Training Network is bringing together 20 partners in academia and industry to explore the impact of the rearing environment and other factors on behaviour and brain function, with the ultimate goal of improving animal welfare.

BAP meeting

The summer meeting of the British Association for Psychopharmacology will take place in London on 19–22 July 2020.

BNS meeting

The spring 2020 meeting of the British Neuropsychological Society will take place on 22–23 April 2020 at the Clinical Neurosciences Centre, Queen Square, London. The Elizabeth Warrington Prize Lecture will be delivered by **Muireann Irish** (University of Sydney).

Developing brain

The Academy of Medical Sciences has published a summary of a two-day interdisciplinary workshop on 'The developing brain in health and disease'. A PDF can be downloaded at **bit.ly/2w0yQD3**.

Recruitment

Mental health research charity MQ has launched a new digital platform, Participate, to address the challenge of recruitment in mental health research. The website (**https://participate.mqmentalhealth.org**) enables potential participants to discover ongoing research projects and what they involve.

Neuroscience@Nottingham

The annual Neuroscience@Nottingham Research and Poster Day took place on 15 January 2020, attended by neuroscientists from across various departments in Nottingham and other institutions. The event kicked off with a workshop on 'Multi-disciplinary approaches to treating anxiety disorders', which brought together research in rat models of fear and anxiety (**Carl Stevenson**, Nottingham) with clinical research (**Naomi Fineberg**, University of Hertfordshire; **Catherine Harmer**, Oxford), as well as with experience of clinical treatment practice (**Fineberg**; **Stephen Regel**, Nottingham).

This was followed by the poster session, where around 30 posters were presented on research ranging from molecular and cellular to cognitive, computational and clinical neuroscience. Two postgraduate poster prizes were awarded to **Samantha Harrison** ('Using fNIRS to assess cortical responses to auditory and visual speech in a paediatric population') and **Sara Goncalves** ('MIA-induced osteoarthritis-like knee pain impacts on cognitive function in Lister hooded rats').

The guest speaker **Catherine Harmer** (Oxford) gave a lecture on 'How do antidepressant drugs work?'. The lecture was preceded by brief presentations highlighting key neuroscience-related initiatives at Nottingham, including the Research Beacon for Precision Imaging and the Interdisciplinary Research Clusters on Technological Innovations in Health and Wellbeing, and on Improving Health and Wellbeing in Contemporary Society. The event was supported by the BBSRC and the BNA.

New funding

Peter Kind, **Adrian Bird** and colleagues in Edinburgh have been awarded £12m funding from the Simons Foundation, extended funding for the Simons Initiative for the Developing Brain from 2022 to 2025.

The Wolfson Foundation has made a £10m award to support a new Wolfson Centre for Young People's Mental Health at Cardiff. The Centre, to be led by **Frances Rice** and **Stephan Collishaw**, will be a dedicated interdisciplinary research centre focusing on reducing anxiety and depression in young people.

The author **J K Rowling** has donated a further £15.3m to Edinburgh to support research on 'the invisible disabilities' experienced by people with multiple sclerosis, such as cognitive impairment and pain. The investment will support new facilities and research at Edinburgh's Anne Rowling Regenerative Neurology Clinic.

A US$7m grant from the **Alzheimer's Association** in the USA will allow UCL researchers to investigate the influence of genetics, health and lifestyle on dementia risk across the life course in 500 members of the 1946 British birth cohort.

Researchers from Edinburgh (**Claire Durrant**) and UCL (**Cara Croft** and **Christy Hung**) have received £1.5m fellowship funding from Sir Jackie Stewart's Race Against Dementia charity, working in partnership with Alzheimer's Research UK. As well as research funding, the initiative provides fellows with opportunities for support from innovation experts at Dyson Technology and Formula 1 motorsport.

European Research Council Consolidator Grants have been awarded to **Tiago Branco** (UCL; Circuit and cellular mechanisms for computing spatial vectors to shelter during escape), **Pleasantine Mill** (Edinburgh; Molecular principles of mammalian axonemal dynein assembly), **Jean-Baptiste Pingault** (UCL; From parental risk to child mental illness: a genetically informed investigation of intergenerational risk pathways) and **Nathalie Rochefort** (Edinburgh; Envisioning the reward: Neuronal circuits for goal-directed learning).

FENS 2020 – The countdown begins

Registration for the 2020 FENS Forum, the European neuroscience event of the year, is now open.

With the FENS Forum coming to the UK for the first time since 2000, the BNA is proud to be the host society of FENS Forum 2020. We have had a hands-on role in developing the exciting and stimulating programme – as well as an unrivalled line up of plenary speakers (see Box), FENS Forum 2020 will feature 56 parallel symposia and more than 3500 abstracts, as well as associated mini-conferences, technical workshops, a grand debate, multiple opportunities for networking, and public events.

Masterclasses

The BNA and the Gatsby Charitable Foundation are sponsoring a range of introductory masterclasses in topical areas of neuroscience, which will be held on Friday 10 July 2020, the day before the start of the FENS Forum.

The courses are being delivered by internationally renowned researchers and build from a broad and easy-to-understand introduction to the latest cutting-edge research. The courses are being held at various centres across Glasgow:

- **Improving mental health and psychiatric disorders: complementary preclinical and clinical research**: University of Strathclyde
- **Credibility of neuroscience: increasing the transparency and reliability of modern-day neuroscience**: University of Strathclyde
- **The microbiome and the gut–brain axis: What is it and why is it important?** University of Strathclyde
- **Manipulating neuronal activity using chemo- and optogenetics**: University of Glasgow
- **Glial cells: Identities, functions and roles in brain health and disease**: Glasgow Caledonian University

For full details and registration information, see **https://forum2020.fens.org/introductory-courses/**

Young Investigator Training Programme

Thirty lucky early-career researchers from around the world will have the opportunity to spend 2–3 weeks before the FENS Forum in a leading UK neuroscience lab, and receive up to €1000 in support costs, thanks to the **Young Investigator Training Programme (YITP)**.

Organised by the Host Society Committee and the BNA, and funded by the International Brain Research Organisation (IBRO), the scheme will enable early-career researchers to undertake a short, focused research project, to build their technical skills and provide networking opportunities.

More than 30 UK-based researchers across all areas of neuroscience have offered to host a visit and have developed mini-projects (see **https://forum2020.fens.org/young-investigator-programme/** for details).

Workshops, mini-conferences and events

A range of specialist workshops will take place as part of the meeting. These focus on optogenetics, large-scale monitoring of neural activity, technologies for studying glial cells, *Drosophila* whole brain connectomics, negotiation skills and career advice.

In addition, eight mini-conferences will be held on Saturday 11 July 2020. These will cover areas such as behavioural neuroscience, cognitive impairment, human brain imaging, neuroeconomics, translational neuroscience, sleep, nicotine and brain development, and a Cajal Club event.

If you would like to get involved in the FENS Forum, there is still time to submit proposals for a satellite meeting or a Forum networking event. Satellite meetings are independent but related scientific events scheduled for before or after the FENS Forum, while networking events are held in the evening during the Forum. The closing date for proposals is 20 April 2020.

Plenary lectures

- **Eve Marder** (USA): Differential resilience to perturbation of circuits with similar performance (Fred Kavli Opening Lecture).
- **Erin Schuman** (Germany): Local protein synthesis in neurons.
- **Sheena Josselyn** (Canada): The amygdala and memory: Recalling the past, imaging the future.
- **Rosa Cossart** (France): How development scaffolds adult hippocampal dynamics.
- **Andreas Meyer-Lindenberg** (Germany): Neural mechanisms of environmental risk for psychiatric disorders (Presidential Lecture)
- **Rui Costa** (USA): Discovering, reinforcing and refining actions.
- **Sonia Garel** (France): Early cortical wiring and neuroimmune interactions (ERA-NET Neuron Lecture)
- **Jan Born** (Germany): Sleep's role in memory consolidation (Tianqiao and Chrissy Chen Institute Lecture).
- **Karl Deisseroth** (USA): New approaches to studying intact brain structure and function (Hertie Foundation Closing Lecture).

Pain: Friend and foe

Pain, the BNA's theme for 2020, is both a medical challenge and a scientific conundrum.

The experience of acute pain might not be pleasant but it serves a vital function, warning us of tissue damage and helping us to learn things to avoid. But when pain persists after initial injuries have healed then it can have a devastating impact on quality of life.

Although the full extent of chronic pain is difficult to judge precisely, it is without question a major medical challenge and a source of misery for millions (see Box). Chronic pain is associated with a wide range of conditions, including cancers, diabetes (diabetic neuropathy), nerve injury, migraine, degenerating conditions such as multiple sclerosis, and musculoskeletal conditions such as rheumatoid arthritis.

In terms of pain control, acute pain can usually be managed effectively. Over-the-counter medicines such as aspirin, ibuprofen and paracetamol enable us to deal with everyday aches and pains. Stronger analgesics are available to clinicians managing more severe pain.

Chronic pain, by contrast, presents a more formidable medical challenge. Some effective drugs do exist but they do not work for everyone and it is difficult to predict which drug a patient is likely to respond to. Furthermore, the risk of dependency is a major issue with some treatments – witness the opioids epidemic in the USA; an estimated 10 million Americans are misusing opioids, leading to the deaths of more than 130 people every day from overdoses in 2016 and 2017.

NOWHERE IS THE PHRASE 'ALL IN THE MIND' LESS HELPFUL THAN IN PAIN – THE EXPERIENCE OF PAIN AND ALL THE FACTORS THAT MODULATE IT EMERGE FROM THE INTERPLAY BETWEEN NEURONS.

A scientific conundrum

As well as being a medical challenge, pain is a complex phenomenon that is only partially understood. Notably, pain can be studied at many different levels. Central to pain are the sensory neurons that detect tissue damage, nociceptors. Much is now known about the ion channels and other signalling molecules that generate pain signals. These molecules are also important targets for the development of pharmacological interventions.

As well as the molecular properties of ion channels, researchers are also studying the activities of nociceptors and of the neural pathways that convey pain sensory to the brain via the spinal cord. Brain imaging studies have revealed much about the networks of brain activity associated with pain.

But pain is much more than just signal and response. Descending pathways can have a significant modulating impact on pain signalling to the brain at the level of the spinal cord. And there is no simple correlation between brain activity and perception of pain. As a result, psychological factors and brain states can have a major impact on the experience of pain. Nowhere is the phrase 'all in the mind' less helpful than in pain – the experience of pain and all the factors that modulate it emerge from the interplay between neurons.

Added to this complexity is the experience of pain unrelated to tissue injury – grief, heartbreak and other forms of mental anguish. The relationship between 'mental' and 'physical' pain is also beginning to be teased apart.

Pain is therefore an ideal theme for the BNA for 2020. It is scientifically fascinating and of great socioeconomic significance. The year kicked off with a pain-related BNA Christmas Symposium – stay tuned for news of more events and initiatives during the year.

The pain of gout, coloured etching, 1835, after J Gillray, 1799.

The impact of pain

- Chronic pain affects between one-third and one-half of the UK population.
- Almost half of people with chronic pain have a diagnosis of depression and two-thirds are unable to work outside the home.
- In 2016, £537m was spent on analgesic prescriptions, with at least an additional 50% cost incurred from the prescription of other drug classes such as antidepressants and antiepileptic drugs.
- The economic impact of pain is high due to absenteeism, poor productivity and people with pain leaving the workforce. In the UK, the annual productivity cost of back pain is estimated to be between £5bn and £10.7bn.
- Painful conditions such as arthritis and back pain account for one-third of all claims for disability benefits in the UK.
- An EU-wide survey in 2017 found that 95 million people across Europe live with chronic pain and the total economic impact of chronic pain was estimated to be as high as €300bn.

Indexing ahoy

Brain and Neuroscience Advances has passed the key PubMed Central assessment – paving the way to full indexing in 2020.

The year began with a bang for *Brain and Neuroscience Advances* with the news that the journal had passed PubMed Central's scientific assessment. To safeguard the quality of PubMed Central, the US National Library of Medicine undertakes a comprehensive assessment of the scientific rigor of journals applying to be indexed and included in PubMed Central. This is the critical step in the application process for indexing – a short technical evaluation is now in progress which should present few issues for *Brain and Neuroscience Advances*' publishers, SAGE Journals.

We therefore anticipate that final approval will be secured in spring 2020. As well as including all new articles, PubMed Central will also retrospectively index all content back to 2017. This will ensure greater visibility of articles and provide a major fillip to the journal.

The positive opinion from PubMed Central is testament to the unceasing labours of Editor-in-Chief Jeff Dalley and his team of Senior Editors, Editorial Board Members, and all the researchers involved in the published content of *Brain and Neuroscience Advances*. We are incredibly grateful to everyone who has devoted time to making *Brain and Neuroscience Advances* a success, including researchers who have submitted papers for publication in early volumes. We are also grateful to SAGE Journals for their efforts in shepherding *Brain and Neuroscience Advances* through the PubMed Central submission process.

"THIS IS AN EXCITING AND IMPORTANT MILESTONE FOR THE JOURNAL AND TESTAMENT TO THE EXTRAORDINARY EFFORTS OF THE EDITORS AND STAFF AT SAGE. I'M VERY GRATEFUL FOR THE UNSTINTING SUPPORT I'VE HAD THROUGHOUT FROM THE BNA OFFICE AND COUNCIL."
Jeff Dalley, Editor-in-Chief, *Brain and Neuroscience Advances*

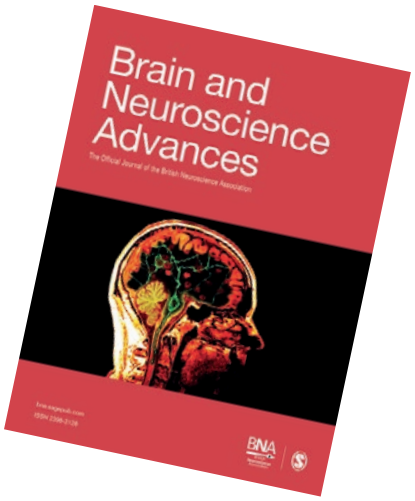
Special collections

A stimulating set of papers will shortly be published in the Special Collection on **neuroinflammation**, overseen by Lead Guest Editor **Kerrie Thomas** (Cardiff) and Guest Editors **Paul Morgan** and **Jeremy Hall** (Cardiff).

A further Special Collection is being developed on fast-acting antidepressants such as ketamine and its derivatives. This Special Collection is being overseen by Guest Editors **Catherine Harmer** (Oxford) and **Mitul Mehta** (KCL).

Another article has also been added to the Special Collection celebrating 50 years of British neuroscience. **Trevor Smart** and **Anne Stephenson** (UCL) provide a fascinating insight into the development of our understanding of GABA, from its discovery as 'factor I' in crustaceans to its current position as one of the most critical neurotransmitters controlling human brain function.

If you would like to contribute to Special Collections, or if there is an area of neuroscience you think would benefit from a Special Collection and would like to be involved in its development, then get in touch with the *Brain and Neuroscience Advances* Editor-in-Chief, **Jeff Dalley** (**jwd20@cam.ac.uk**).



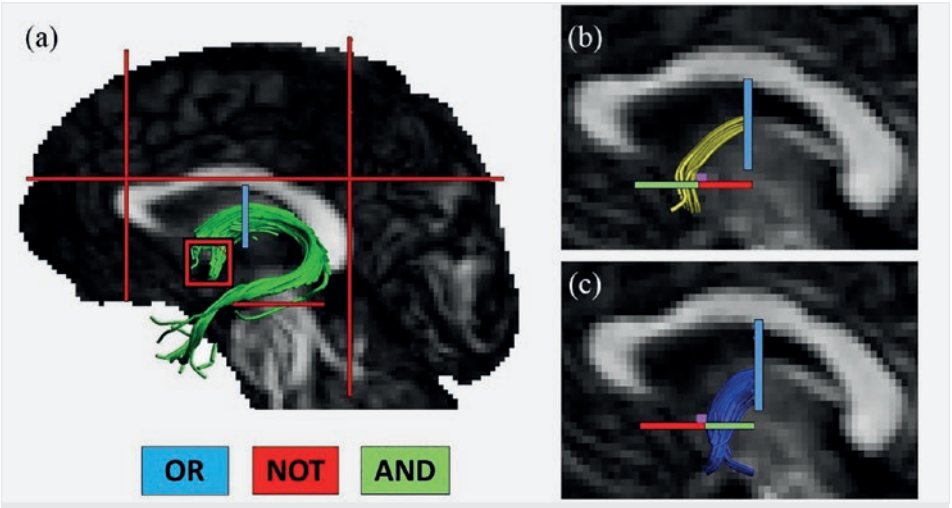
Glasgow bound

Brain and Neuroscience Advances will also have a presence at FENS 2020 in Glasgow in July. Professor Dalley will be taking part in a Special Interest Event at lunchtime on Sunday 12 July, 'How society-owned journals handle your paper', alongside editors from *Neuroscience*, the *Journal of Neuroscience*, and the *European Journal of Neuroscience*.

Newly published

Claudia Metzler-Baddeley (Cardiff) and colleagues have published novel *in vivo* neuroimaging evidence for distinct microstructural properties of pre-commissural and post-commissural fibers in the fornix, a key structure in the hippocampal complex (see Figure).

It what seems like the blink of an eye, we are already onto *Brain and Neuroscience Advances* volume 4. All content is freely available at **https://journals.sagepub.com/home/bna** and full details on how to submit a manuscript can be found at **https://journals.sagepub.com/author-instructions/BNA**.



Projections from the rat hippocampal formation (from Mathiasen *et al.*).

Pain gain

Though focused on pain, the BNA Christmas Symposium was a festive pleasure.

The BNA Christmas Symposium attracted more participants than ever to its new venue at Bush House on the Strand, formally the home of the BBC World Service but now occupied by KCL. As is now traditional, the Symposium provided an opportunity to introduce the BNA's theme for the coming year, pain.

Irene Tracey (Oxford), the brains behind the programme, provided a brief introduction to the field, and raised some of the points due to be discussed by **Joanna Bourke** (Birkbeck) who was unfortunately unable to attend. Pain is a complex phenomenon, triggered by nociceptors in the periphery detecting tissue damage but characterised by complex patterns of processing in the brain which give rise to the subjective experience of pain. As well as neural signalling, this experience is also influenced by sociocultural factors – including religious interpretations of suffering and the supposedly character-enhancing properties of physical adversity.

Professor Tracey distinguished acute pain, which helps us to detect and avoid threats to health, from chronic pain – pain that persists after initial injury. While we all think nothing of a popping a paracetamol, chronic pain is notoriously difficult to treat.

However, **Peter McNaughton** (KCL) described promising work that may lead to a new treatment option. Chronic neuropathic pain reflects repetitive firing in nociceptors after nerve damage. HCN ion channels play a key role in controlling firing rate in cardiac muscle cells, and Professor McNaughton has identified

PAIN IS A COMPLEX PHENOMENON, TRIGGERED BY NOCICEPTORS IN THE PERIPHERY DETECTING TISSUE DAMAGE BUT CHARACTERISED BY COMPLEX PATTERNS OF PROCESSING IN THE BRAIN WHICH GIVE RISE TO THE SUBJECTIVE EXPERIENCE OF PAIN.

a nociceptor-specific HCN channel, HCN2, that may be a 'pacemaker of pain'. Ivabradine, an HCN antagonist, has analgesic properties, but lowers heart rate alarmingly. His group has developed a compound that is specific for HCN2 and has shown great promise in pre-clinical models. Rights to the compound were sold to Merck for US$340m.

Bridget Lumb (Bristol) focused on descending pathways, which have the capacity to modulate pain signals from the periphery. With Richard Apps, she has been exploring interactions between the periaqueductal grey and the cerebellum, in a more systems-wide perspective that integrates motor responses to painful stimuli.

Lesley Colvin (Dundee) brought a clinician's view of pain. Chronic pain is common – affecting 18% of people in Scotland – and difficult to treat. Although most patients will respond to a treatment, it is currently difficult to predict in advance which option would be most appropriate. Dr Colvin pointed to the current difficulties in assessment; better methods would help to identify those at risk of chronic pain and help to stratify treatments. Dr Colvin also discussed the challenge of long-term use of opioids, a major health crisis in the USA. Prescribing of opioids has begun to decline in Scotland, but unfortunately use of illegal opioids has increased in response, as has use of other treatments such as gabapentinoids, which have been responsible for an increasing number of deaths.

Beginning with an unconventional approach to treatment adopted by Hugh Laurie in *House* – kidnapping a patient and forcing him to undergo mirror box therapy – **Tamar Makin** (UCL) focused on the perplexing challenge of phantom limb pain. People who undergo amputations commonly maintain the perception of the lost limb, which often feels painful. This has traditionally been thought to reflect loss of inputs from the amputated limb to the somatosensory cortex, followed by 'invasion' of surrounding areas into what were that limb's cortical areas. The mirror box treatment is designed to reverse this process. However, Dr Makin's work has revealed that somatosensory cortical areas appeared to be preserved to a much greater degree than previously thought.

Rarely, people are born without the ability to sense pain. As **David Bennett** pointed out, such people are often seen as curiosities – as illustrated by the 'human pincushion', Edward Gibson, who in the 1920s would insert needles into his face in the cause of entertainment. Mutations in several genes are now known to cause insensitivity to pain, such as PRDM12 and Nav1.7, and generally disrupt the function of nociceptors (although mutations in a FAAH pseudogene influence pain perception by altering endocannabinoid production). As well as providing insights in to the mechanisms of pain signalling, identification of such genes also provides leads for drug development.

Ulrike Bingel (Essen) discussed the remarkable power of the placebo effect to modulate pain. Key to its success, she suggested, were expectancy and beliefs and conditioning/learning, emphasising the key importance of context and the patient–practitioner interaction. Although lying to patients is ethically questionable, a deeper understanding of how placebo effects work could inform approaches for maximising the likelihood of treatment responses. Remarkable, though, even 'open label' placebo studies have shown statistically significant positive effects.

Keith Phillips (Eli Lilly) noted that

pain was a challenging area for drug development, with a very high failure rate. Important ways forward could include greater focus on patient-based target selection, patient stratification, and validation of biomarkers for assessing treatment effects and ensuring that treatments actually engage with targeted biological systems in the ways envisaged. He described a range of biomarkers being developed for different points in the pain pathway.

Switching to pleasure, **Siri Leknes** (Oslo) provided a thought-provoking presentation on opioids. She noted that their effects were more complex than often assumed. Work with agonists and antagonists suggests that they have some impact on reward responsiveness, reduce pain and stress (particularly cortisol levels) but have little or no impact on mood. Perhaps surprisingly, agonists are often not seen as a particularly pleasant experience (often the reverse) – although eliminating pain is very blissful. Professor Leknes suggested that the effects of opioids were very variable, with only a proportion of users likely to progress to addiction and users representing a very distinct group.

Continuing the theme of illicit drugs, **Val Curran** (UCL) discussed latest findings on cannabis. She pointed out that cannabis contains more than 140 cannabinoid compounds, although most attention has focused on Δ9-tetrahydrocannabinol (THC, which generates the cannabis high) and cannabidiol (CBD). THC and CBD are the yin and the yang of cannabis, the former being associated with most of its ill-effects and the latter being protective and possibly even therapeutically useful. Unfortunately, use of high-THC versions of cannabis such as skunk is increasing. Evidence of CBD's role in pain relief is less clear – while US medical authorities are relatively positive, attitudes in the UK are more ambivalent.

The meeting finished with a wide-ranging discussion touching upon the challenges of the placebo effect for drug development, whether the placebo effect could be harnessed in clinical practice, and whether industry pessimism about drug development for pain was justified. The importance of individual differences was stressed – in laboratory animals as well as people. The speakers also contributed to a special edition of BBC Radio 4's *All in the Mind*, presented by Claudia Hammond.

Finally, three game students bravely took part in a test of the placebo effect, being fooled into thinking that an affordable white wine was an expensive red – a perfect segue to unblinded wine tasting at the post-symposium reception.

PRIZE-WINNERS

The Christmas Symposium as also the time when the annual BNA awards are handed out. This year's eminently deserving winners were:

Outstanding Contribution to Neuroscience 2019: Steve McMahon

Professor McMahon is Sherrington Professor of Physiology at KCL and directs the Wellcome Trust Pain Consortium. He has long been one of the world's leading researchers studying the molecular mechanisms of pain and nurturing the next generation of UK pain researchers.

Postgraduate award 2019: James Phillips

(Cambridge; see page 34).

Undergraduate award 2019: Pia Siegele

(Edinburgh; see page 34)

Public Engagement of Neuroscience 2019: Dean Burnett

Dean Burnett is a neuroscientist, lecturer, author, blogger, podcaster, pundit, science communicator, comedian and numerous other things, depending (he says) on who's asking and what they need. Previous a lecturer at Cardiff, Dr Burnett is currently a full-time author. His 'Brain Flapping' column appeared in the *Guardian* from 2012 to 2018 and his book *The Idiot Brain* was published by Guardian Faber Publishing.

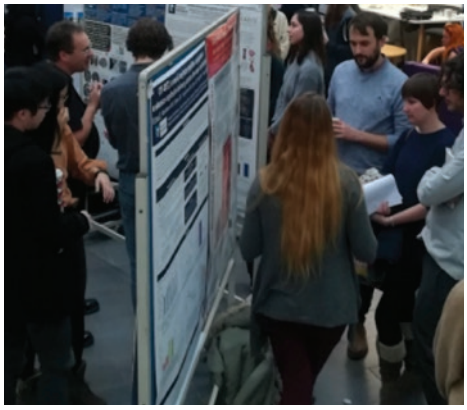
Out and about

Notable events and people in the BNA world.

Speakers at the **formal launch of the BNA's credibility manifesto at the House of Commons** included Lord Winston and Dorothy Bishop.

The BNA team had a strong presence at the **Bristol 'Neuro Nets' meeting** aiming to strengthen connections between the neuroscience and psychiatry communities.

Carl Stevenson, Catherine Harmer and Stephen Regel discuss anxiety at the **Neuroscience@Nottingham Day 2020**.



Harry Devito made good use of his last half-term, producing this rather splendid model of a nerve cell. It looks good enough to eat.

Out and about

The **Seventh Cambridge Neuroscience Symposium**, Artificial and Biological Cognition (ABC2019), attracted a large and engaged audience (and two selfie-taking BNA staffers...).





'**David Marr: 50 years on**' was an ABC2019 satellite meeting marking the seminal contributions of David Marr to neuroscientific thought. Cambridge Neuroscience coordinator **Dervila Glynn** (below left, centre) is shown with the meeting speakers.


Out and about

Chas Bountra (far left), Pro-Vice-Chancellor, Innovation, represented Oxford at the official signature ceremony for the European University of Brain and Technology, NeurotechEU bid led by Tansu Celikel at Radboud University on 24 January 2020. The ceremony also included a panel discussion with the rectors of the eight founding universities which was chaired by Kia Nobre, Chair of the Oxford Neuroscience Strategy Committee.

Neil Harrison (Cardiff) delivered the Hodge Centre for Neuropsychiatric Immunology's annual Public Lecture, 'Inflammation and depression: Too much of a good thing?', to a sell-out crowd on 21 November 2019.

Jane Haley (Edinburgh Neuroscience Scientific Coordinator and BNA Local Group Rep) was presented with an MBE by HRH The Princess Royal at Buckingham Palace on 29 January 2020. Coincidentally, Princess Anne also presided at Jane's UCL graduation ceremony in 1987.

Getting to know your BNA

Name: **Elena Toma**
Job title: **BNA Outreach Ambassador**
Joined the BNA: **September 2019**

Role in a nutshell

My main role is working on the BNA's new education programme, consisting of neuroscience materials to provide neuroscientists with 'tool-kits' to support outreach. My main project is to evaluate this programme. Lydia and I deliver neuroscience outreach sessions in schools and I am currently working on my own modules – Drugs & Addiction and Speech & Language. I am very excited to be delivering outreach sessions in schools and collecting data to determine the effectiveness of the programme! My role also involves keeping the website updated with jobs, events and news articles, as well as helping at internal and external events and with other admin and communication tasks.

Why did you apply for a placement at the BNA?

The BNA is a fantastic organisation that really emphasises the importance of raising awareness of neuroscience and how it is relevant to everyone. I really wanted the chance to be a part of this and dedicate my year in industry to helping in public engagement and promoting neuroscience research.

What's your dream job, and why?

I'm not sure exactly what my dream job is yet, but I have had a lot of volunteering experience working with many different types of people and that is something I really enjoy. Through my placement, I have developed a passion for outreach and science communication, so perhaps something along those lines. I would love to be able to deliver outreach sessions in schools as a full-time job. I am also considering roles such as a physician associate, as working within a multidisciplinary team, and directly with patients, really appeals to me – hopefully in a neurology unit.

What's the best thing about working at the BNA?

I love delivering neuroscience sessions in schools because I think raising awareness and enthusiasm of neuroscience in young people is really important. It's so rewarding to see young students engage, get excited and ask lots of interesting questions about neuroscience and what it's like to study neuroscience at university. Plus the executive team here at the BNA are very welcoming and supportive – being a part of the team has been one of the best things about this placement year.

What do you get up to when you're not being BNA Outreach Ambassadors?

I love travelling, hiking and rock climbing, and generally being outdoors. I enjoy life drawing and pottery too, which for me are the best ways to relax and unwind. I am also a volunteer committee member for the Bristol Hub Schools Plus programme, which trains and coordinates students as volunteer tutors in schools with the aim of tackling educational poverty.

Name: **Lydia Bown**
Job title: **BNA Outreach Ambassador**
Joined the BNA: **September 2019**

Role in a nutshell

Generally, helping where help is needed! There are regular admin jobs I do, as well as posting on our social media channels and website. I'm often involved in writing and creating various resources for the BNA, from writing an article for the website highlighting research published in the our journal, to putting together gift vouchers for those who wish to give membership as a gift, or editing videos we've produced about neuroscience. One of my main roles is to engage with our Associate Members and grow the work we do for them, which has involved putting together the new Associate eBulletin each month. I also work closely with Elena on the BNA's education project.

Why did you apply for a placement at the BNA?

Having done some outreach and public engagement before, and being passionate about engaging people in science, I was really excited about getting involved in the work the BNA does to increase public awareness of neuroscience research. It was also a great opportunity to have hands-on experience of how a scientific society works; to see all the behind-the-scenes work which goes into the BNA's projects and enables us to support and represent neuroscientists and neuroscience research.

What's the best thing about working at the BNA?

It's been such a great experience to come into a team of lovely and talented people, to be able to work alongside them and to be given real responsibility and the opportunity to get stuck in to different projects. Being a small team, we work closely with each other and it's brilliant to see how the skills of different people come together to achieve the great things the BNA does. It's also rewarding and exciting to be able to see one's ideas and suggestions being quickly talked through and put into action.

What's your dream job, and why?

For a summer while I was at sixth-form college I volunteered at the National Marine Aquarium in Plymouth and loved it, especially giving talks to the public and chatting to people of all ages about the marine life in the aquarium. It would be amazing to have a job where I'm able to engage people in science in a similar way, while being able to do some writing (which I've so enjoyed during my placement) and to use my creativity on some interesting projects.

What do you get up to when you're not being BNA Outreach Ambassadors?

I love a cycle ride in the countryside or a long walk, especially in late spring and early summer when the swallows and house martins are around, but at the moment I'm having lots of fun going to salsa classes!

Bright Brains
Newsletter

Issue No. 14
Spring 2020

Welcome to the spring edition of our 'Bright Brains' Newsletter! This edition is very special because it is the last edition I will be editing as founding chief editor. 'Bright Brains' was launched five years ago to give a voice to the BNA's young members, and it has been a pleasure and a privilege to be able to turn the vision of 'Bright Brains' into reality.

Half a decade later, with a total of 112 print articles, 63 online articles produced by 81 writers, 80 editors and 50 contributors, 'Bright Brains' has been successful in helping young members become vocal about their views. On behalf of the entire 'Bright Brains' team, I would like to thank the BNA for making 'Bright Brains' a great success. The BNA has recognised the importance of its young members' contributions to science communication, and the role they play in positioning neuroscience as a science that leads to a better understanding of how we can improve lives.

Below are quotes on how 'Bright Brains' has made a difference to contributors, with complete quotes available in our online section. In this edition, our 'Nuntia' section reveals how you can increase your motivation, and it explores the link between cognitive decline and air pollution. Our 'Socialia' section highlights the changes to neuroscience in the context of open science. Our 'Varietas' section shows how volunteering can add another dimension to our understanding of neurodegenerative diseases, and uncovers what kind of diet can help you preserve normal brain function in old age. It also tells you how neuroimaging can be used together with Bayesian optimisation, and provides information on how fear inhibition is mediated in the brain. 'Numquid sciebas...?' illustrates how electrophysiological methodologies can help network neuroscience develop new therapies, while 'Quid novi?' evaluates the health effects of foods that are high in nitrate. Finally, we sincerely hope that you will have as much joy in reading our final 'Bright Brains' newsletter as we had in producing it!

Jayanthiny Kangatharan,
'Bright Brains' newsletter coordinator

Bright Brains: A big thank you

As this is the final issue of 'Bright Brains' that Jayanthiny is editing as founding chief editor, we would like to take the opportunity to thank her and her team of editors and contributors, for all their hard work putting together issues over the past few years. To date, 'Bright Brains' has more than succeeded in its aim of giving a voice to early-career neuroscientists, with ever-interesting, informative and entertaining articles.

Early-career researchers and students remain a key group for us at the BNA and we'll continue to include a special section within the Bulletin to highlight material from young neuroscientists in future issues. We're currently consulting on the best way to achieve this, with content that will best reflect the interests and concerns of researchers in the formative stages of their careers. We're aiming to have something new and ready to go in the summer.

In the meantime, thanks again to all the 'Bright Brainers' - your efforts have been greatly appreciated.

Anne Cooke, BNA Chief Executive

"**Editing** the work of others is possibly **more valuable to my development as a science communicator** than my own writing, and **gives me greater confidence when writing** myself." **Jack Cooper**

"**Contributing as an editor**, I have enjoyed being updated on new and upcoming trends, **leading to stimulation of many thought-provoking discussions amongst my peers**, alongside **reviving** the importance of both **inter- and multidisciplinary perspectives**." **Aisha Islam**

"In every submission, there is a value-adding process where **we contribut**e to a product that is always better than the original draft with the **ultimate purpose of advancing the standards of our research community. Innovation starts here**." **Marco Travaglio**

"My editorial role with **Bright Brains undeniably helped me to become a more succinct scientist**, something I'm immensely grateful for." **Ryan Stanyard**

Marco Travaglio
PhD student in Neuroscience,
University of Cambridge

Neuroscience of motivation and how to improve it

What is motivation? It is an invigorating force that enables you to act, whether it is to get out of bed or to sign the much-awaited contract that will shape the rest of your career. Dopamine has emerged as a key neurotransmitter involved in almost every aspect of motivation. It conveys its signal by passing from one neuron to the next through the 'mesolimbic pathway', otherwise known as a neuronal circuit that connects the middle of the brain (midbrain) to its outermost region (cerebral cortex). Dopaminergic neurons originate from the ventral tegmental area (VTA), from where they project to the nucleus accumbens as well as to other 'limbic' regions such as the hippocampus and to prefrontal cortex.

While the earliest experiments were thought to suggest that dopamine regulates our ability to perceive pleasure and reward, it was not until recently that this idea was overturned to show that dopamine activity may actually be related to human motivation instead. Recent experiments showed that animals with lower levels of dopamine opt for the low-value, easier-to-obtain reward whereas animals with higher levels of brain dopamine would show increased motivation to work harder to obtain the high-value reward. Regarding where in the brain dopamine exerts its effects, consensus revolves around the idea that high levels of dopamine in the nucleus accumbens will encourage you to tick every box of your to-do list whereas low levels will leave you sprawling in your bed.

So what can we do to improve our motivation? Train your brain. Researchers suggest that our brain can be trained to create the right dopamine environment and one way to do this is by anticipating the reward. Visualise the completion of a project and embrace the perceived reward from completing the task. Using real-time brain-imaging techniques, neuroscientists have found that reward information is processed in the prefrontal cortex and that this area interacts directly with the nucleus accumbens and VTA to trigger motivated behaviour. What this means is that anticipated reward can directly influence your willingness to work by activating the very key brain motivation centres.

But ultimately, while neuroscience certainly helps to hack our biological constraints, we should not forget that old-school self-discipline and determination are two of the most powerful forces to boost your motivation. Much research is needed to fully understand the complex biological mechanisms that generate and maintain our willpower but, in the meantime, passion and perseverance into whatever you are doing will probably get your dopamine flowing. The rest will follow.

The full article with references can be found at: **www.bna.org.uk/publications/bright-brains/bb-online/**.

Rachel Jones
Graduate student in Neuroscience,
University of Leeds

Air pollution: a risk factor for Alzheimer's disease?

Environmental awareness surrounding climate change has become an increasingly common topic of discussion among politicians, the media and general public alike. Currently, the effects of air pollution on the central nervous system (CNS) are being investigated, in particular its involvement in the development of Alzheimer's disease.

One of the first examples of a link between air pollution exposure and cognitive decline, the primary characteristic of Alzheimer's disease, was reported in 2008 in Mexico City. Healthy children in Mexico City with no known risk factors for cognitive dysfunction exhibited hyperintense prefrontal white matter lesions and significant deficits in cognitive tasks, compared with their clean-air counterparts. These results gained traction and inspired a range of subsequent studies reporting similar findings. Adults exposed to long-term high levels of air pollution tend to show significant deficits in verbal memory, attention and episodic memory compared to less exposed adults. The trend of results even suggested that each 10 $\mu g/m^3$ increment increase in particulate matter (PM, particles suspended in air pollution) concentration that adults were exposed to was equivalent to cognitively ageing by approximately 2 years.

Researchers consequently hypothesised that long-term PM exposure could be a risk factor for the development of Alzheimer's disease. Incomplete knowledge of disease progression, plus the potential to modulate environmental risk factors (unlike genetic risk factors), provided motivation to take research further. Abnormal Aβ deposition, hippocampal neuronal atrophy and upregulation of proinflammatory mediators are present in the brains of both highly exposed humans and animals. These are all well-established hallmarks of Alzheimer's disease. Most recently, a study carried out in London reported a positive exposure–response relationship between air pollution and incidence of Alzheimer's disease diagnosis in adults with no recorded history of dementia, unexplained by confounding factors. Our ageing population will naturally result in increased financial and emotional burdens on society, stemming from age-related diseases including Alzheimer's disease. In a 'two-birds-one-stone' approach, being mindful of our environmental impact and reducing levels of air pollution could help mitigate these burdens. Further research is imperative to obtain concrete evidence of links between air pollution and Alzheimer's disease, potentially influencing environmental policy changes worldwide.

This article together with references can be found at: **www.bna.org.uk/publications/ bright-brains/bb-online/**.

Marta Blanco Pozo
PhD student in Neuroscience,
University of Oxford

The open access dilemma

From making code and data available to publishing in open access journals, a great effort is currently being made to promote open science and to make research accessible to everyone. Major funding bodies, including the Wellcome Trust, are now updating their policies to align with 'Plan S', which is "an initiative to make full and immediate Open Access to research publications a reality". This means that from 2021, all scientific research findings must be published in open access journals or platforms. But do we know how this will affect both senior and early-career researchers?

To address this question, the Cortex Club – the Oxford University Neuroscience Society –organised a panel discussion on open science and open access. We invited Elisa de Ranieri, editor at *Nature Communications*, John Inglis, co-founder of bioRxiv and medRxiv and executive director at Cold Spring Harbor Laboratory Press, Sally Rumsey, Head of Scholarly Communications and Research Data Management at the Bodleian Library, and Mark Patterson, executive director of *eLife*.

We started by discussing how journals, institutions and repositories are improving the way research is being published and shared, how subscription fees are increasing at a higher rate than university funds, and how universities and institutions could support publishing in open access journals. Then, the focus of the debate shifted to the impact that open access might have on researchers' careers.

Some institutions like Oxford have signed the San Francisco Declaration on Research Assessment (DORA), which states that the impact factor from journals should not be used to assess quality research or in the hiring process. However, this declaration has not been signed by all research institutions, and a recent meta-analysis showed that 40% of research universities in the USA and Canada explicitly mention that journal impact factor can be used for tenure and promotion evaluations. Does this mean that publishing in open access journals with lower impact factors rather than renowned closed journals could jeopardise early career researchers' futures or make it difficult for more senior researchers to keep their positions?

All of the panellists agreed on the complexity of this issue. Moreover, a way to assess research quality aside from a journal's impact factor has not been established yet. In brief, the research community needs to continue discussing these issues, and find new ways to address them. Initiatives such as Plan S are certainly changing research publishing culture. However, the way this will affect researchers at different career levels and institutions is still to be determined.

This article together with references can be found at: **www.bna.org.uk/publications/bright-brains/bb-online/**.

Ryan Stanyard
PhD student in Neuroscience, KCL

Open Science: Changes to Neuroscience

In recent years, both neuroscience and the psychological sciences have witnessed a call for a robust framework to provide online materials that better enable scrutiny of research. This will help guard both the validity of financial investment in research and mark a stand against publication bias and credibility inflation. Previous media scrutiny has ousted pioneers in psychology, discredited for fabricating data, using convoluted methodologies to mask the absence of true results and misleading readers.

Far more commonly but less dramatically and undermining for the public, a paucity of published materials and data has contributed to what has been termed the 'replication crisis'. This term was popularised largely in the psychological literature but it is also relevant to neuroscience and the medical sciences. Neuroscientists have endeavoured to provide better access to both raw and processed data in addition to other research materials. Similarly, neuroscience has begun to introduce registered reports in line with new guidelines, a framework common in international and multicentre protocols for imaging or genomic studies, among others. Nonetheless, the transition to replicable science is not progressing without difficulty.

In 2019, a year in which the BNA Festival of Neuroscience (Dublin) and the meeting of the Organisation of Human Brain Mapping (Rome) were celebrated, we have also seen papers exploring themes such as neural oscillations in artificially re-perfused porcine tissue gracing the likes of *Nature*. Yet, equal strides in fundamental changes to research and publication structure are under way. The introduction of the open science and registered reports frameworks is becoming lucrative to many stakeholders. These platforms are enabling researchers to critically review changes to methods and flag gaps in planned analyses. Alleviating the focus from high-impact publishing in the wake of the Research Excellence Framework and the archaic pyramid scheme in academic advancement, this new approach provides better means of appraising bids for funding high-expenditure research projects and acknowledges the merit of peer scrutiny.

Adjustment to new terms in this arena may be daunting. There may be questions as to how early-career researchers will engage with pre-published or pre-print materials or how they will convince principal investigators opposing the movement. Open science advocates for more transparent, supportive scrutiny of peer-reviewed literature prior to, during and following formal publication. Ultimately, this gives more credibility to neuroscience research.

This article together with references can be found at: **www.bna.org.uk/publications/bright-brains/bb-online/**.

Tamsin Nicholson
Graduate student in Neuroscience,
University of Glasgow

Why every neuroscientist should volunteer

During my master's, I developed an interest in neuroinflammation and chose to do my research project in a pre-clinical multiple sclerosis lab. I loved my research and its potential to help people. But it was years before I realised what I had been missing.

A while later, I decided to volunteer in a local care home. Here I met Sue: bubbly, friendly and fiercely independent. Only in her 60s, she is one of the youngest residents and she acts like it. She tells me about her fundraising plans for Alzheimer's UK; she is going to shave off all her hair because the skydiving company refused to let her do a jump! Sue has an amazing sense of humour, she enjoys her gym sessions and always gets involved with care home activities. She tells me about the hazards of baking when you have multiple sclerosis and how cakes have ended up on the walls and floor after a spasm. She makes light of her disabilities, as someone who has accepted them and learnt to live with it all.

I have learnt a lot from my time with Sue. I have learnt about the power of positivity, and that there is always so much more to a person than their disease. But I have also come to appreciate what it means to keep some independence when your body begins to fail you. While a cure for multiple sclerosis would be transformative, the little things can make a huge difference. Whether it is finding a way for Sue to complete her skydive, or to be able to eat peas without them rolling all over the floor, these small steps mean a lot.

Mileha Soneji is a product designer who has come up with some amazing tools to help people with Parkinson's disease. She combined her design skills with her first-hand experience of her uncle's disease to create simple yet effective aids for people with Parkinson's, such as a 3D printed staircase to help people walk smoothly on flat surfaces. As a neuroscientist, you can set yourself up to innovate, too. Combining your scientific knowledge with first-hand experience of the disease could help you bring about simple innovations that really do change lives.

Translational research has become increasingly prominent in recent years, but translation is still something that a lot of scientists struggle to achieve. By volunteering, you can get that experience to help you take something from bench to bedside and to make a real difference. But even if you take that out of the equation, ask yourself: how much can you really understand a disease without understanding the people who live with it?

Marco Travaglio
PhD student in Neuroscience,
University of Cambridge

Food for your brain: The Mediterranean diet

Historians used to call it the 'cradle of civilisation' but for many scientists today the real value of the Mediterranean basin does not lie in its contribution to history. Accumulating evidence suggests that feeding your brain with the plant-based diet of the olive-growing Mediterranean regions may reduce the risk of cognitive problems, effectively making you live a longer and healthier life. In 1999, as part of a broader investigation into the prevalence of several diseases in older adults, researchers at the University of Bari discovered that individual elements of the Mediterranean diet are protective against cognitive decline. This pioneering work demonstrated that a large intake of mono-unsaturated fatty acids, abundant in olive oil, is protective against cognitive decline.

Encouraged by these intriguing results, scientist Valls-Pedret and colleagues at the Barcelona's Institut d'Investigacions Biomèdiques August Pi Sunyer embarked on the first-of-its-kind clinical trial looking at the association between a Mediterranean diet and cognitive function in older individuals. Results were striking. After several years of data (and food) crunching, researchers demonstrated that participants allocated the Mediterranean-style diets display improved learning and memory whereas those allocated a normal diet show signs of cognitive decline. But how does a Mediterranean diet exert its effect on the brain? Most experts suggest that its mysterious effects could stem from the abundance of anti-oxidant agents that it provides. Oxidative stress is often cited as major cause of cell damage in several age-related brain conditions and is caused by the accumulation of toxic compounds in the brain called free radicals. With time, excessive accumulation of free radicals can lead to the irreversible loss of brain cells, which can profoundly affect learning and memory. Complex substances with important anti-oxidant properties such as olive oil, wine, nuts, fruits and vegetables are present in high concentrations in the Mediterranean diet, suggesting that these substances may reduce oxidative processes in the brain, preserving normal brain function.

Nonetheless, while mounting research points to the beneficial effects of the Mediterranean diet on brain health, more research is needed to prove its effects. Most studies suggest a link between this diet and brain function but little is known about the mechanisms that drive its effects on the brain. In addition, defining minimum quantities of recommended foods remains a priority. Researchers agree that there are lots of benefits and no known downside to following a healthy diet. However, while adding olive oil and mixed nuts to your diet may benefit your brain cells, using excessive amounts will only make you gain weight. So... don't go nuts!

This article in full together with references can be found at: **www.bna.org.uk/publications/bright-brains/bb-online/**.

Ryan Stanyard
PhD student in Neuroscience, KCL

Bayesian optimisation

In conventional structural and functional MRI, image acquisition is led by radiographers (or researchers in some institutes). Subjects are scanned according to study protocols, adjusting parameters for the size of the subjects' brain volumes. A series of pre-planned scans are to be completed within a confined scanning window, which in many studies is typically around 1 hour. Efficient acquisitions often employ parallel imaging techniques (using spatial localisation techniques to reduce phase-encoding steps during acquisition, and effectively reducing scan times). These technologies can be co-utilised alongside a Bayesian optimisation approach; rather than scanning an entire subject's brain/'volume' according to protocol, subjects are scanned at increasing resolutions in sub-sampled regions of interest or indeed the whole brain. Next, this individual's scan is compared in real-time against a database of normative typically developing healthy controls, matching for resolution, age and other stratifiers of interest (e.g. sex, disease severity), yielding a dynamic and flexible approach. By comparing in-scan subjects against normative populations for given tasks, the algorithm can derive which tasks/areas an individual is most 'different' from relative to a normative sample, guiding subsequent acquisitions.

This is useful for several reasons. First, individuals with low tolerance for MRI (e.g. people with claustrophobia, who are hyper-anxious or physically/mentally disabled or have attention-deficit hyperactivity disorder) do not need to undergo less important scans and can complete either more relevant runs of a task/paradigm or finish early. Second, this approach means scanning can focus on tasks/areas of interest. Finally, in totality, this approach would deliver lucrative cost savings. Given conventional imaging costs ~£400-600 per hour, whether commercially, for research or clinically, shorter scan times could potentially deliver huge savings for bodies such as the NHS. Conversely, scans from conventional imaging are routinely anonymised (personal data are redacted) and so can be used by other researchers to bolster modelling normative distributions if technical specifications match their own sampling strategy.

This article together with references can be found at: **www.bna.org.uk/publications/bright-brains/bb-online/**.

Andreea Pantiru
PhD student in Neuroscience,
University of Leeds

Fighting to forget

Fear is an emotional experience deeply ingrained in evolution to foster survival and enable avoidance of potentially harmful conditions. However, fear may become dysfunctional and result in anxiety and trauma-related disorders, such as post-traumatic stress disorder (PTSD). Exposure therapy is the main approach to combat PTSD, but 40% of patients fail to respond to this therapy. Fear encoding is not fully understood; therefore, development of better treatments requires an improved comprehension of how fear is processed in the brain. Fear extinction is a learning mechanism, which manifests in a decline in fear responses towards a stimulus that was previously eliciting fear. Extinction is essential for understanding fear-related disorders as it is the process upon which exposure therapy is based. But how can we target this extinction process?

Fear conditioning is a well-established technique, which helped identify the amygdala as a key structure of the brain involved in the formation, consolidation and extinction of fearful memories. This learning paradigm represents the coupling of an event, the conditioned stimulus (CS), with an aversive event, the unconditioned stimulus (US). Even one CS–UC pairing is sufficient to elicit a fear response to CS alone. CS-dependent fear can be diminished through subsequent repeated and unreinforced re-exposure to the CS, which leads to fear extinction. Enhancing fear extinction could potentially ameliorate disorders, such as PTSD, by inhibiting the intrusive recollection of traumatic experiences.

The basolateral nucleus of the amygdala (BLA) contains two electrophysiologically distinct populations of neurons: one that is activated during acquisition and one activated during extinction of fear. Research revealed that thymus cell antigen 1 (Thy1) is distinctively expressed in extinction cells, which mark a population of glutamatergic neurons within the BLA. Activation of Thy1 neurons in the BLA blocked the transmission of fear-related signals to downstream areas, important in regulating physiological and behavioural consequences following fear exposure, and revealed a role of Thy1-expressing BLA neurons in fear circuitry. Behavioural analysis showed that optogenetic inhibition of BLA Thy1-expressing neurons during fear conditioning/extinction results in increased fear responses, while chemogenetic activation of these neurons reduces fear-related behaviours in mice, highlighting the importance of Thy1 neurons in extinction.

Overall, these studies emphasise the significant role that Thy1-expressing BLA neurons play in mediating fear inhibition and provide insight into a new potential target for fear disorders, such as PTSD. A better understanding of how fear is encoded will ultimately lead to efficient biologically driven approaches for treatment and prevention of fear-related disorders.

This article together with references can be found at: **www.bna.org.uk/publications/bright-brains/bb-online/**.

VARIETAS NUMQUID SCIEBAS...?

Jeremy Chabros
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In search of a Rett syndrome treatment

Rett syndrome is a childhood disorder leading to cognitive and motor impairment. It is the second most common cause of severe intellectual disability worldwide. Although it currently remains without a cure, recent advances in network neuroscience might aid the emergence of novel therapeutic strategies.

Network neuroscience has been the mainstay for elucidating how functional connections are established during neurodevelopment. The vast majority of evidence in this field comes from non-invasive imaging studies, such as resting-state fMRI or magnetoencephalography. However, although these methods enable evaluation of network topology and activity, they require time, resources and volunteers.

Electrophysiological experimental methods, such as multi-array electrode (MAE) recordings, bridge the gap between cellular and network neuroscience. *In vitro* recordings from human dissociated cortical cultures are more ethical than animal studies, more closely resemble conditions that occur during human neurodevelopment, are more cost- and time-effective, and enable genetic and/or pharmacological intervention.

The majority of Rett syndrome cases involve a mutation in the *MECP2* gene. Among its myriad of roles, the Mecp2 protein influences the switch between Glu2NB and Glu2NA NMDA receptor subunits, differentially affecting receptor deactivation kinetics in parvalbumin-positive interneurons and pyramidal cells. Loss-of-function of Mecp2 leads to disrupted wiring of cortical circuits and defective network activity. Using drugs that act preferentially on NMDA receptors with pathological subunit compositions points to a possible way through which functional connectivity could be protected.

As NMDA receptors play a pivotal role in synaptic plasticity, MAE studies can also help to explore the nature of this mechanism. Moreover, this approach can be used to study other disorders of the nervous system. Indeed, it is applicable wherever pathology influences network topology or function. The inherent assumption, however, is that the changes occurring at the network level *in vitro* can recapitulate the events *in vivo*. Although this might only be true in certain situations, using such systems will, nonetheless, accelerate basic and translational research in such cases.

This article with references can be found at: **www.bna.org.uk/publications/bright-brains/bb-online/**.

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Beetroot and the brain

In a culture of miracle cures and quick fixes, we are constantly bombarded with sensationalist headlines of fad diets that promise instant weight loss or nonsensical health improvements. Having to weave through headlines, blogs and celebrity endorsements of a new cancer cure or super-drug can make it difficult to know whether any of these claims bear any real weight or evidence base.

A diet that has a growing body of evidence of health benefits is a high-nitrate diet. Nitrates are a common constituent of our diets found in abundance in fruits and vegetables, particularly in beetroot and green leafy vegetables. Dietary nitrate increases the systemic availability of nitric oxide, which in turn regulates several physiological processes that improve cardiac blood flow and exercise tolerance.

Evidence of the beneficial effects of beetroot juice, which contains high amounts of nitrate, was first demonstrated in a study by Webb *et al*., which showed that beetroot juice reduced blood pressure. Another study showed that beetroot juice supplementation improved efficiency and performance of athletes in cycling and marathon runners. Similarly, The Dietary Approaches to Stop Hypertension study showed that a 'combination diet' high in fruit and green leafy vegetables reduced blood pressure and decreased risk of ischaemic stroke and coronary artery disease.

The beneficial vascular effects of dietary nitrate in preventing and treating neuro-vascular disease are currently being explored. Bondonno *et al*. found that higher vegetable nitrate was associated with a decreased carotid artery wall thickness and a 17% lower risk of stroke. Another study showed that a high-nitrate diet improved cerebral perfusion in frontal lobe white matter, critical areas that degenerate in dementia.

Fad diets come in and out of fashion on a weekly basis. So far, evidence suggests that eating beetroots, or a diet high in nitrate content, can reduce your cardiovascular risk and improve exercise tolerance. However, further high quality research needs to be conducted regarding whether beetroot is a viable treatment for stroke or dementia prevention. Until then, at the risk of sounding sensationalist, there is no harm in grabbing a beetroot juice the next time you are out brunching with your friends.

This article in full with references can be found at: **www.bna.org.uk/publications/bright-brains/bb-online/**.

Answers to the crossword from Issue 13 – Autumn 2019
Horizontal 3: pTau; 4: MCI; 5: AD; 7: HDAC inhibitors; 8: PD; 9: GWA; 10: Lumbar puncture.
Vertical 1: Medial Amygdala; 2: Entorhinal cortex; 6: PTSD.

Pain – from molecules to minds

Genetic approaches are revealing new targets for treatment of neuropathic pain.

Neuropathic pain, persistent pain triggered by damage to somatosensory neurons, is common, debilitating and difficult to treat. As well as running a peripheral neuropathy clinic in Oxford, **David Bennett** is investigating the genetic and other factors contributing to neuropathic pain – work that could lead to more targeted and effective treatments.

Inspired by modules on pain in his intercalated BSc, Professor Bennett secured a Wellcome Trust scholarship to work with legendary pain researchers Pat Wall and Steve McMahon. By chance, he had the opportunity to stand in for the latter on a placement at Genentech in San Francisco. Bitten by the research bug, on his return, he enrolled on a PhD with John Priestley and Professor McMahon.

Unusually, therefore, he embarked on a PhD – on the role of neurotrophic factors in pain – before he had even started his clinical training. He went on to finish his clinical training and served his time as a junior doctor. "But I'd enjoyed research so much I'd always wanted to come back to do more pain research."

A Wellcome Trust fellowship enabled him to complete his clinical training and set up his own lab at King's College Hospital. Shortly after becoming a consultant, he moved to Oxford in 2012. Although challenging, he is convinced that combining clinical work and research is an advantage. "I'm seeing people with difficult neuropathic pain week in week out. A lot of the research questions I try to answer derive from clinical issues that I've seen and as much as possible I want to take the research back into the clinic. There's a lot of cross-fertilisation between the two and that's where I try to position myself, to work at that translational boundary."

The genetics of pain

Over time, Professor Bennett has come to specialise in the genetics of pain. Identifying the abnormal genes that cause inherited conditions involving either

"WE'VE GOT A LOT MORE TARGETS AND A LOT MORE UNDERSTANDING OF HOW DYSFUNCTIONAL NEURAL CIRCUITS LEAD TO CHRONIC PAIN, WHICH WE HOPE WILL TRANSLATE INTO NOVEL THERAPIES."

insensitivity or extreme sensitivity to pain has revealed key components of pain systems, including the Nav1.7 voltage-gated ion channel (product of the *SCN9* gene). Mutations in Nav1.7 alter its ion transporting properties and the electrical excitability of pain-sensing neurons (nociceptors), in some cases leading to hyperexcitability and chronic pain. Notably, several Mendelian pain disorders have been tracked to abnormalities in ion channels. Nociceptor hyperexcitability may therefore be a common feature of neuropathic pain, although Professor Bennett suspects that it is unlikely to be a single entity: "There are going to be many pathophysiological drivers."

Mendelian disorders with extreme phenotypes are very rare and may not necessarily be relevant to more common pain conditions. The past decade or so has seen explosive growth in genome-wide association studies (GWAS), which scan entire genomes to identify genetic variants that are more common in patients than in controls and may therefore be involved in disease.

However, the impact of GWAS in pain has been limited. "It's been difficult to apply to pain, partly because you need quite large well-phenotyped cohorts," says Professor Bennett. "We're only just starting to see those results come through now." Furthermore, identification of genetic associations is often only the beginning of the story. "They're often in regions of the genome that have regulatory functions," points out Professor Bennett. They may therefore not affect the structure or function of a protein but where and when it is made, and it may not be obvious how a variant is contributing to susceptibility to pain.

Whatever their source, genetic leads can be followed up in functional studies. Abnormal ion channels, for example, can be expressed in cultured cells and their properties explored. Mutations can be 'knocked in' to create animal models. But a particularly powerful technique now is to generate induced pluripotent stem cells from patients and differentiate them into somatosensory neurons in culture for functional studies.

At a glance

- Chronic pain linked to nerve damage (neuropathic pain) is common and often hard to treat.
- Identification of genes causing inherited pain disorders has revealed key proteins involved in chronic pain and new targets for drug development.
- Major initiatives are underway to deeply phenotype and stratify patients to support more personalised treatment.

Clinical understanding

As the GWAS studies illustrate, the diversity of neuropathic pain presents a major challenge – for clinical practice as well as research. Although some effective drugs are available, they do not work for all patients: "When sitting with a patient in front of us, we don't really know what would be the most appropriate drug for that patient."

The answer lies in more intensive phenotyping. In the landmark DOLORisk study, for example, Professor Bennett and colleagues are following a cohort of 10,000 people from across Europe at risk of neuropathic pain. Notably, data collection spans a wide range of neural, biological, demographic and psychosocial factors. "Then you can begin to piece together how one relates to the other."

The longitudinal cohort approach

Wellcome Images

Chronic pain, tormenting devils: Coloured etching by J Cawse, 1809, after G M Woodward.

can reveal factors associated with the emergence of neuropathic pain. Although data collection is ongoing, insights are already emerging. Interestingly, points out Professor Bennett, "Psychology has a massive modulatory role." Patients with susceptibility to depression, anxiety, or prone to catastrophising are more likely to develop neuropathic pain.

This could lead to unhelpful suggestions that their problems are 'all in their mind'. But, points out Professor Bennett, that's exactly what pain is anyway – the experience of pain reflects central brain activity even if nerve damage is peripheral. Moreover, he adds, "The brain doesn't passively receive the signals coming into it; there's also a top-down pain modulatory circuit that can either facilitate or sometimes suppress information at the level of the spinal cord."

As well as DOLORisk, Professor Bennett is also working with UK Biobank, whose 500,000 participants are providing detailed medical data, lifestyle information and biological samples, undertaking more extensive phenotyping of people with or at risk of neuropathic pain. Such work could reveal biomarkers enabling those at particular risk of neuropathic pain to be identified and supporting stratification of patients, so clinicians can tailor treatments to individual patients: "That's something that we could deliver in the short term."

In the longer term, new treatments are urgently needed: "Of course, what we would like is new analgesic drugs that are more effective and have fewer side effects." It is possible to block pain signals, for example using the anaesthetic lidocaine. However, lidocaine is not a practical treatment – it has to be applied locally as it shuts down all neural activity.

Single gene studies have enabled some patients to be treated with drugs targeting their abnormal ion channels. More generally, they have revealed potential targets for drug development, and recent work has revealed signalling components specific to nociceptors: "If we could find a means of selectively silencing nociceptors, then that would be extremely helpful in terms of treating neuropathic pain."

Although some drugs for neuropathic pain are in clinical trials, it has been a challenging area for drug development, with a depressingly high failure rate. Professor Bennett is hopeful that recent work may help to overcome the perception that neuropathic pain is too 'hard': "We've got a lot more targets and a lot more understanding of how dysfunctional neural circuits lead to chronic pain, which we hope will translate into novel therapies."

Professor Bennett therefore remains upbeat, and doesn't regret the extra effort that combining clinical training and research has required: "It was a challenge, no doubt about it. There were times when I thought life would be simpler if I was doing one or the other, but I have to say I always enjoyed integrating the two and it was worth it in the end."

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Hundreds and thousands

Neuropixels technology is enabling recordings to be made from tens of thousands of neurons – revealing a surprising picture of brain activity.

Recording from electrodes has been the mainstay of neurophysiology for decades. As the technology has improved, the number of neurons from which recordings can be made has gradually increased. Now, an international research consortium including **Matteo Carandini** (UCL) has developed new tools that look set to revolutionise the field.

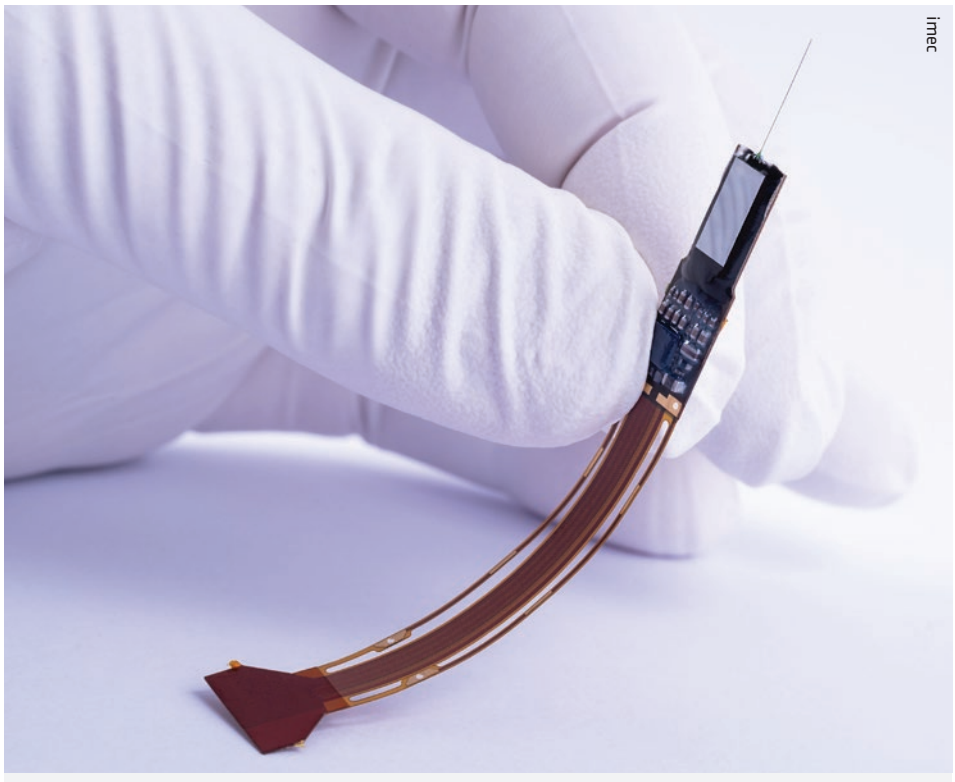
Professor Carandini highlights the key role played by Tim Harris, a Howard Hughes Medical Institute (HHMI) senior fellow at HHMI's Janelia Farm Research Campus: "He realised that the kind of electrodes that laboratories were using round the world to record from the brain were based on 1980s technology." In other fields, technology had come on in leaps and bounds: "The technology we carry on our mobile phones is way way way superior."

Professor Harris made contact with a not-for-profit semiconductor company in Belgium, imec, which has the only ultraclean nanofabrication facility in Europe. It has a strong research and development focus and had already developed innovative solutions for the ATLAS collaboration at CERN.

imec were keen to help: "They said they could build a new probe that instead of having just a few sites of recording on the shank that is inserted in the brain, it would be way thinner and have 1000 recording sites."

Although technically feasible, the development costs would be high given that the anticipated market is specialised and relatively small. Professor Harris therefore put together an international consortium, which was able to secure funding from sources including the HHMI, the Allen Institute for Brain Science in Seattle and Wellcome (via UCL).

"I HAD TO LEARN LOTS OF NAMES OF BRAIN REGIONS THAT I DIDN'T EVEN KNOW EXISTED."



imec

A first-generation Neuropixels probe.

This support enabled imec to develop version 1.0 of the Neuropixels probe, and also to sell it at cost price. Affordability was a key goal, and Neuropixels technology can be adopted by labs even with modest funding. Importantly, very little additional technology is required: "Once you have them, you barely need a lab," says Professor Carandini. "What comes out of them is already digital and could be plugged into a laptop. It's a big democratiser of neurophysiology."

The second key development has been new software tools to manage the streams of data generated by Neuropixels probes. With hundreds of detectors, each neuron's activity is likely to be picked up by five to six electrodes. The distinctive properties of each neuron's outputs, however, provide a way to match signal to originating neuron – spike sorting – and to locate the position of active neurons. Software tools have been built that automatically achieve spike sorting almost in real time: "That has made it possible for lots of labs to use them – without this it would have been really hard."

Scientific insights

Following the development of version 1 of the Neuropixels probes, the first papers resulting from their application were published in 2019. Karl Deisseroth and colleagues recorded from 20,000 neurons in studies of the signals underlying thirst. And Professor Carandini, his colleague Ken Harris at UCL and their international collaborators published a paper in *Nature* describing the results of visual processing studies recording from 30,000 neurons. "These are crazy numbers," points out Professor Carandini. "My PhD thesis was about 50 neurons."

Professor Carandini's particular interest is in decision-making informed by vision. The new technology has had a transformative impact on his work. Previously, researchers would specifically target their areas of interest: "Now instead

you put these electrodes in and you record from a lot of brain regions you might not think you're interested in because they happen to be along the path. And then you analyse the data and you realise very often there are very interesting signals in parts of the brain that you didn't think you were interested in."

Importantly, this approach has provided a radically different view of brain function: "We discovered that the signals underlying decision-making are much more distributed across the brain than we thought." Neuroscience textbooks perpetuate the idea that functions in the brain are neatly parcelled into different regions. This may well be misleading, says Professor Carandini: "They give the impression that there's a fantastic division of labour. The division in brain regions, at least in the mouse, it's strongly supported by genetics and anatomy, but it's not very well supported by physiology or activity, in that there seem to be neurons distributed around the brain that seem to do things that are very similar even though they are in different regions."

This revelation was apparent in both the pioneering Neuropixels papers: "Both of them indicate that things are much more distributed than one would have thought."

One consequence, says Professor Carandini, is that he has suddenly had to become acquainted with some of the quieter backwaters of the brain, like the zona incerta: "I had to learn lots of names of brain regions that I didn't even know existed."

Furthermore, the signals in these unexpected locations do not appear to be just noise or coincidental: "The signals are way cleaner and more repeatable than anything I've ever seen."

The future

With Neuropixels being picked up by more than 200 labs, work has begun on the successors to version 1.0. Professor

The tip of the Neuropixels probe.

"WE DISCOVERED THAT THE SIGNALS UNDERLYING DECISION-MAKING ARE MUCH MORE DISTRIBUTED ACROSS THE BRAIN THAN WE THOUGHT."

Carandini is leading a team developing version 2.0, which will be lighter, smaller, have four shanks rather than one, and will be more amenable to long-term implantation so data can be recorded for weeks or months at a time.

Other groups are exploring the potential for use in primates or humans, although their small size, perfect for rodents, is a drawback when it comes to species with larger brains.

There is also scope to increase recording capacity still further. "The limits are due to the widths of the wires," says Professor Carandini. Neuropixels wires are 190 nm wide, but those in mobile phones go down to 6 nm – but at a cost: "Your mobile phone gets very hot."
At the moment, the product specification for Neuropixels probes is for a maximum increase of 1°C to avoid overheating the brain. But there is little if any basis for this threshold: "We don't know yet how much we can warm up the brain. This specification could be too conservative – we don't know."

Alongside this development work, Professor Carandini and several colleagues from UCL – Ken Harris, Michael Häusser, Sonja Hofer, Peter Latham and Tom Mrsic-Flogel – have joined a global consortium, the International Brain Laboratory, to systematically address brain function using Neuropixels technology. Consortium members are standardising behavioural techniques and parcelling out regions of the brain to study, much like the Human Genome Project distributed chromosome to different labs for sequencing. This avoids duplication of efforts and greatly enhances the amount of data available. With data freely available, a new generation of neuroinformatics researchers may never generate data themselves but just work on the mountains of data freely accessible in global databases.

All these efforts reflect a collaborative approach that has seen competitors join forces to advance the field cooperatively: "It's been a big success of open science," says Professor Carandini.

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Non-trivial pursuit

A deeper understanding of the neurobiology of curiosity could have important implications for areas such as education.

Overwhelmed by curiosity: Alice through the looking glass.

Following his undergraduate studies in Germany, **Matthias Grube**r (a Sir Henry Dale Fellow at Cardiff funded by Wellcome and the Royal Society) moved to UCL for his PhD on learning and memory. Rather than the traditional approach of examining brain changes associated with learning and memory, he wondered whether the brain's initial state had any impact on subsequent learning. "And we found out it actually does."

The key finding was that motivation to learn enhanced learning and memory recall. However, motivating participants in research studies usually means providing opportunities for them to gain financial rewards. During his postdoc at the University of California Davis, Dr Gruber began to wonder how realistic these paradigms were. He realised that intrinsic interests were strong motivators for learning: "It's actually about your interest, your curiosity, which shapes what you learn and what information you seek in daily life."

An emerging field

Despite its importance to human behaviour, curiosity remains surprisingly under-studied, in neuroscience at least. In part, this may reflect a degree of uncertainty about what it actually is: "We don't really have an agreed definition of curiosity," admits Dr Gruber.

Psychology has a longer history of exploring curiosity, mostly focused on 'trait curiosity' – curiosity as a permanent personality characteristic. However, Dr Gruber is more interested in 'state curiosity' – temporary changes in the brain indicative of someone being curious about something.

Dr Gruber's work has principally focused on exploring how state curiosity affects brain activity and its impact on learning and memory. The most commonly used method to elicit curiosity is through trivia questions, which to varying degrees trigger an interest among participants to discover the answer.

Reducing uncertainty

One advantage of working in the field of learning and memory, suggests Dr Gruber, is that much is already known about the neural pathways involved, including those that enhance learning. In addition, past work in psychology has generated a rich literature on curiosity. Against this backdrop and drawing on his own findings, Dr Gruber has developed the first neuroscientific model of curiosity: "We tried to bring all these theories of curiosity that are out there in psychology together to map it onto brain systems."

The PACE (prediction, appraisal, curiosity and exploration) model is rooted in the classic principle of the prediction error. A prediction error can arise when something unexpected, new or unusual appears in the external environment, generating sensory impacts that do not match expectations. This perspective highlights the importance of structures such as the hippocampus, known to have a role as a kind of novelty detector.

Internally, information may arise that is incompatible with existing concepts, leading to cognitive conflict. This kind of situation is associated with activity in the anterior cingulate cortex (ACC).

However, activation of these systems does not automatically trigger a state of curiosity: "We think there is a mechanism in between, a prefrontal mechanism, that is evaluating or appraising information and then it leads to curiosity," says Dr Gruber.

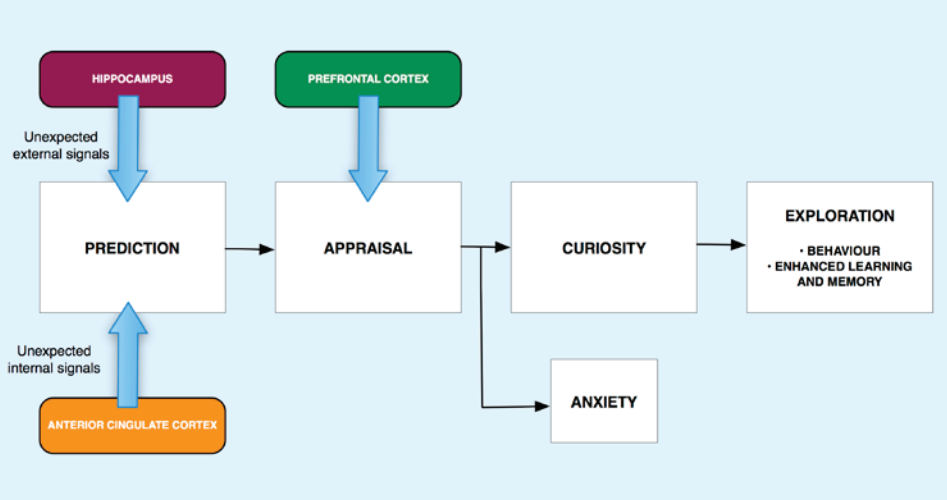
The involvement of the prefrontal cortex is critical in determining the response to prediction errors. On the one hand, it can drive actions to find out more to resolve uncertainty. "Or it could be the complete opposite – something that's very novel, something that eliciting lots of internal cognitive conflict, could also lead to anxiety."

If the prefrontal cortex points us in the direction of discovery, dopaminergic pathways are then engaged. "Then basically people are more active to seek out

At a glance

- Curiosity reflects the internal motivation to seek out new information.
- A curious brain state enhances learning and memory consolidation.
- The Prediction, Appraisal, Curiosity and Exploration (PACE) model provides a framework to guide the neuroscientific study of curiosity.

"WE TRIED TO BRING ALL THESE THEORIES OF CURIOSITY THAT ARE OUT THERE IN PSYCHOLOGY TOGETHER TO MAP IT ONTO BRAIN SYSTEMS."



A simplified version of the PACE model of curiosity. Adapted from Gruber and Ranganath, 2019.

information," says Dr Gruber. In addition, strong inputs into the hippocampus lead to enhanced memory encoding.

Total recall

One of the most striking of Dr Gruber's findings is that curiosity also enhances learning of incidental information – a kind of spillover effect of an enhanced learning state. For example, if participants are shown incidental faces while undertaking the trivia question test, their memory for those faces is greater when their curiosity has been piqued: "We were really surprised by that," says Dr Gruber. "We thought it was risky and probably wouldn't work. And then it did work."

A reviewer of their paper was also sceptical, and suggested that they check the results by testing memory a day later. "We thought, this will never work out. We ran the experiment, and the results were very clear." Memory for faces presented during high-curiosity states was still significantly greater a day later.

This result was important, as it implied that memory consolidation as well as encoding is enhanced by curiosity. This may distinguish curiosity from another well-studied phenomenon, attention. "We definitely think curiosity is related to attention: curiosity enhances attention during encoding. But it must be more than attention, because it enhances memory consolidation processes as well." In ongoing functional imaging studies, Dr Gruber is trying to tease apart brain activity shared by attention and curiosity and unique to each.

What's the point?

A bigger question is why we are curious anyway. "That's the key thing about curiosity – there's no immediate benefit of it." Acquiring mountains of knowledge might make someone a whizz at Trivial Pursuit, but it also absorbs the brain's precious resources. From an evolutionary perspective, curiosity may have provided a selective advantage: "Just knowing your environment better might help you in the long run." However, as any cat will testify, curiosity can be a dangerous thing, so balancing pressures would have acted to keep curiosity in check.

These arguments apply to trait curiosity, but the underpinnings of state curiosity remain equally unclear: "We assume it's a good thing – it's a good thing for learning and memory, but we don't really know why. It's very early days in the research field still."

Dr Gruber sees several potential implications of research on curiosity. Several conditions are associated with abnormalities in dopaminergic systems, such as depression and apathy, which could have implications for curiosity. In addition, stimulating curiosity could be a way to enhance learning and memory recall in those with memory impairments, such as people with Alzheimer's disease.

But perhaps the greatest impact could be in education: "That's what excites me the most," says Dr Gruber. Young people today face an uncertain future and the possibility of jobs yet to be invented. It is not clear what skills and knowledge they will need. "We need to help them to become lifelong learners, raise them to be curious citizens with active learning skills with excitement about learning and embrace this new era where you continuously learn about new things and educate yourself."

While much of his past research has been on young adults, he has also begun to explore the impact of curiosity on learning and memory in children and adolescents. Early findings suggest that while curiosity promotes learning and memory in both groups, surprise at the answers gives a further boost to memory only in adolescents. He has also begun to investigate curiosity and memory within virtual reality environments and in computer games.

Dr Gruber has come a long was since his days as a postdoc when he had to win over his initially sceptical supervisor. The challenge was even greater as his initial pilot studies flopped. "It took some time to convince him it was an area worth studying," says Dr Gruber. "But I thought, 'this is such an important topic, it's completely understudied, I need to find a way to study it'. That's really what kept me going."

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Positive feedback

Neurofeedback could provide a way to improve management of chronic pain.

Nerve injury can have a devastating impact, leading to major disabilities and paraplegia. On top of that, patients with nerve damage are at significant risk of chronic neuropathic pain. With a background in engineering, **Aleksandra Vučković** is exploring whether technological solutions – specially, EEG-based neurofeedback – could help patients better control their pain.

Based in the School of Engineering in Glasgow, Dr Vučković has been working with clinicians Matthew Fraser and Mariel Purcell at Queen Elizabeth National Spinal Injuries Unit in Glasgow on brain–computer interfaces to aid rehabilitation. The University of Glasgow has funded a dedicated research space within the Spinal Injuries Unit, the Scottish Centre for Innovation in Spinal Cord Injury, in which researchers from different universities in the west of Scotland work together.

This work had focused her attention on activation of the motor cortex. However, during her PhD in Aalborg, Denmark, she had work alongside a large pain group, and was aware that pain was also associated with abnormalities in cortical activation that could be detected by EEG.

Functional imaging studies have demonstrated that chronic pain is associated with increased activation of the sensorimotor cortex. Dr Vučković was able to show that EEG could also detect this abnormal brain activation: "When we ask people to imagine movement, we see that people who are about to develop pain or are in pain have much strong activity in motor cortex." Notably, activation patterns differed between paraplegic patients with and without pain, suggesting they were related to pain rather than disability.

The reason for the study was her interest in using EEG signatures of pain as the basis of a neurofeedback intervention. In such approaches, participants are presented with visual representations of EEG brain activity and, through practice, learn how to modulate brain activity, receiving real-time feedback through the visualisations. Neurofeedback is showing promise in several treatment areas, including epilepsy and anxiety.

Learning to use the neurofeedback equipment.

Having secured MRC funding, Dr Vučković travelled to London to gain training in neurofeedback techniques. As an engineer, she was able to save money by building her own equipment and, with her PhD student, set about trialling the technique on patients in Glasgow.

Neurofeedback is not an instant fix, but Dr Vučković was fortunate that her study group included people with a medical background, teachers and others keen to try something new to control their pain: "We had very motivated first participants, we were very lucky with that."

Drawing on the earlier study, participants were shown coloured bars sensitive to activity in the alpha, beta and theta frequency ranges, those most associated with pain. The alpha band was given greatest prominence, as it appears to be the one most strongly linked to pain. The size and colour of the bars shifted in line with EEG recordings.

Initial results were highly promising. Six out of seven patients in the pilot study experienced statistically significant reduction in pain, and four patients reported clinically relevant reduction in pain (>30%) which lasted at least a month after treatment. These figures are comparable with the results of pharmacological treatments.

The Inspire Foundation was sufficiently impressed with the findings that it funded a project to develop a set-up usable by patients and caregivers in their own homes. An initial usability study found that 15 out of 20 participants were able to use the neurofeedback equipment and 12 out of the remaining 15 were able to modulate their brain activation. Pain reduction was statistically significant in 12 participants and clinically relevant in eight. Nine participants reported a high level of satisfaction with the intervention.

The mechanistic basis of neurofeedback interventions is poorly understood. Participants are taught to relax, but relaxation alone does not seem to be sufficient to modulate brain activity. Dr Vučković is co-supervising a PhD student who is investigating the psychological factors affecting the success of the technique and patients'

At a glance

- Chronic neuropathic pain is associated with abnormal activation of the sensorimotor cortex.
- Through neurofeedback, patients can learn to modulate abnormal cortical activity.
- Reduced activity of the sensorimotor cortex is associated with clinically significant pain relief.
- EEG signals can also identify patients with spinal injuries who are risk of chronic neuropathic pain.

SIX OUT OF SEVEN PATIENTS IN THE PILOT STUDY EXPERIENCED STATISTICALLY SIGNIFICANT REDUCTION IN PAIN, AND FOUR PATIENTS REPORTED CLINICALLY RELEVANT REDUCTION IN PAIN (>30%) WHICH LASTED AT LEAST A MONTH AFTER TREATMENT.

The views of participants

"THIS TRAINING IS LONGER THAN I WOULD DO MY RELAXATION AND IT HAS AN IMMEDIATE EFFECT IN TERMS OF LOWERING PAIN. WHAT IS NEW FOR ME IS THAT THERE IS SOME RESIDUAL EFFECT THAT LASTS THREE TO FOUR DAYS FOLLOWING TRAINING WHERE THE PAIN LEVEL IS LOWER AND DIFFERENT TO WHAT I WOULD NORMALLY EXPERIENCE".

"SPASMS AT WORK HAVE DIMINISHED GREATLY. AND I MEAN GREATLY. AND I'VE ONLY JUST CLICKED THAT IT'S SINCE I'VE STARTED USING THIS [BCI–NFB] THAT WHEN I PUT THE HEADPHONES ON AT WORK, THE SPASMS DIMINISH".

"ANOTHER THING I ALSO GOT OUT OF THE RESEARCH IS JUST BEING IN CHARGE OF THE PAIN. PRIOR TO THIS THE PAIN CAME AND IT WAS THERE AND I COULDN'T DO MUCH ABOUT IT. AFTER THE RESEARCH I FELT I COULD CONTROL THE PAIN. I WAS IN CONTROL AND THE PAIN DOESN'T HAVE TO BE IN CHARGE OF YOU, YOU CAN PUSH THE PAIN BACK."

mentalising strategies. It appears that many participants focus on pleasant episodic memories. Personality traits may also be important – the technique appears to be more effective in those who have the strongest sense that they have agency over their lives. Indeed, a commonly stated benefit mentioned by participants is that they now have a greater sense of control over their pain.

Adrian Wressell/Wellcome Images

Spinal injuries can lead to pain as well as loss of movement.

Predicting pain

A further area of interest for Dr Vučković is the evolution over time of changes in the brain and the experience of pain. To this end, she established a cohort of new spinal injury patients. "We looked at people early after injury, before they develop pain, and for 6 months follow up."

By comparing signals from patients who went on to develop pain from those who did not, Dr Vučković was able to discern brain activation signatures that were predictive of the development of neuropathic pain. Using a machine learning approach, she has developed a classifier that can detect those at highest risk of developing chronic pain.

This raises the possibility that neurofeedback could be used preventively, to block the development of pain. However, Dr Vučković has found that people soon after injury, when not affected by neuropathic pain, are generally not motivated to use neurofeedback. In part, this reflects a limited understanding of the nature of neuropathic pain – most patients see pain as an acute affliction that can be controlled by drugs and will fade when injuries heal. In addition, patients may suddenly be facing a dramatic change in their circumstances: "If somebody ends up on a wheelchair, they're so overwhelmed they can't really focus on pain on top of that."

Dr Vučković has now begun a larger study to explore early signatures of pain, recruiting patients from both Glasgow and the National Spinal Injuries Centre at Stoke Mandeville. A key aim is to develop a tool that will help clinicians assess patients and identify those at risk of chronic pain. "Ultimately what I would like to make is something that doctors can easily use in neurology departments with existing 19-channel devices that they have in hospitals."

She is also keen to secure funding for a larger randomised controlled trial of neurofeedback in spinal injury patients. But she is also interested in exploring the potential of neurofeedback in other groups of patients experiencing chronic pain where EEG abnormalities have been observed, such as multiple sclerosis and post-stroke patients.

Neurofeedback has some way to go before it becomes a routine treatment for pain. But Dr Vučković has found it highly rewarding to receive positive feedback from patients. "Me and my students are so really happy when we find that it works for somebody."

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Right place, right time

Irene Tracey has run a functional neuroimaging unit, a university department and an Oxford college. Highly successful by any measure, her career has not followed any grand plan but has been based on being curious, loving science, people and seizing opportunities as they present themselves.

Having been evacuated during the war, Professor Tracey's parents had little educational opportunities themselves but greatly valued education and encouraged learning: "It was an incredibly supportive home life," she recalls. And, from her earliest years, she had the hallmarks of a future scientist: "I was always really curious, and I was probably a bit of a pain growing up, constantly asking 'why?', 'why?', why?'." Fortunately, she had five older siblings to pester.

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She excelled at her local comprehensive school, and had a particular affinity for maths and physics: "It wasn't that I was bad at the others, it was just those I found effortless." Notably, she suggests, skills in these areas were more widely beneficial: "There's this natural overspill, everything becomes much easier."

Although specialising in the physical sciences at A-level and having a particular interest in astrophysics, the life sciences were still an option. Work experience convinced her that medical training was not for her and her chemistry teacher introduced her to biochemistry: "I'd never even heard of it," she says.

Given her academic prowess and its outstanding reputation in biochemistry, Oxford seemed a natural choice. Professor Tracey thrived in Oxford, yet a career in science was far from certain. Nevertheless, exposure in lectures to leading scientists and their research was inspirational

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– particularly one given by Professor Sir George Radda on the emerging technology of *in vivo* magnetic resonance spectroscopy (MRS): "I was like, 'wow, I need to do that'." She realised it would give her an opportunity to use her physics and maths expertise, applied to biological mechanisms. "I thought, 'this is a win-win, this is everything I love'."

After a lab placement in her fourth year, she stayed in Oxford for a PhD, again with George Radda (after a year out spent, among things, working in a Belgian chocolate shop, travelling and playing hockey). To start with, she explored muscle tissue in boys with Duchenne muscular dystrophy. But the gene affected, dystrophin, is also normally expressed in the brain, and her supervisor was happy for her to change tack. A landmark paper followed and sparked an interest in neuroscience: "I thought, the brain is a hell of a lot more interesting than skeletal muscle, I think I want to go into that."

The birth of brain imaging

It was fortuitous that the opportunity to work with George Radda came as MRS was being introduced into biology, and increasingly neuroscience. Timing was also perfect for her next move. In Harvard, researchers were combining Sherrington's early ideas linking blood flow and brain activity and Radda's magnetic resonance work relating changes in relaxation times of water (in plasma) to the oxygenation state of blood – notably the change in ratio of paramagnetic to diamagnetic iron within haemoglobin as it loses but then delivers oxygen to feed active neurons: "All these ideas were known but this lab in Harvard had put it all together and did the first functional imaging experiments to look at

Irene Tracey.

the brain in action." This was the birth of fMRI – and Professor Tracey wanted to be right there at its dawn.

Her work initially focused on changes in the brains of people with HIV infections and AIDS. But serendipity brought her to the field for which she is best known: "Coffee room conversations led to a chance meeting and a chat with the pain clinic at Massachusetts General Hospital and the struggles they have with trying to understand pain – what is it, how do we know what is going behind the scenes, the challenges of only having someone describe it."

Professor Tracey was intrigued: "This is a huge topic which had everything I loved. It had basic discovery science, it had all this clinical relevance, it was philosophical – It had everything."

Oxford had also been making plans to jump aboard the fMRI bandwagon, and Professor Tracey had been identified as key to the future of its brain science research. With her mother being diagnosed with Alzheimer's disease, she

returned to Oxford earlier than planned to help support her family. As well as building a highly successful research programme in pain, she helped to establish the Oxford Centre for Functional MRI of the Brain and became its second director, for ten years, before taking on responsibility as Head of the over-arching department, the Nuffield Department of Clinical Neuroscience.

Learning to lead

Despite not having thought greatly about career advancement, Professor Tracey took to leadership like a duck to water. "You don't seek it out, as an academic it gets thrust upon you," she suggests. "We all do our good citizenship in making the system work because it's self-governing. In that zeitgeist you need to step up and take on some of these roles, whether it's running an imaging centre or a department."

She adds that she was fortunate to have incredibly supportive colleagues and heads of department, men and women, encouraging her progress – people like Paul Matthews, Kay Davies, Angela Vincent and Chris Kennard. In turn, she aims to mentor the younger generation, particularly female scientists. Leadership roles can seem quite daunting, but she tries to encourage women to give it a go: "You never quite know whether you're going to like it or whether you're going to be good at it."

In Professor Tracey's case, she discovered that she did have a flair for strategy and leadership: "And I really enjoy it. I genuinely find it very rewarding to make things happen, to create physical buildings or cultures where I can see people realise their full potential. That may sound clichéd or corny but that is honestly true: I just find that very fulfilling."

Which is not to say that things haven't been challenging. In Boston, Professor Tracey married her fiancé from Oxford (Myles Allen, an atmospheric/climate physicist who joined her in Boston and worked at MIT) and upon returning to Oxford they started a family. She was helping to care for a mother with dementia and an ageing father. She is well aware that her achievements relied significantly on family support: "I could only do that because my husband was willing to and wanted to take on the lion's share of raising the kids."

"IT'S A PRIVILEGE TO BE ABLE TO DO WHAT WE DO. I DON'T SEE IT AS A THING I HAVE TO COUNTERWEIGHT LIFE AGAINST... I HAVE THIS MIX OF THINGS I ENJOY DOING, AND AT DIFFERENT POINTS IN ONE'S LIFE THIS COMPOSITE CHANGES."

With three children, Professor Tracey would manage the morning school run and her husband the evenings. Her elder siblings also provided valuable support. The secret, she suggests, is to be aware that compromises and sacrifices would have to be made: "I was very clear that I couldn't have it all, I absolutely didn't have that expectation; I recognised that there would be sacrifices and compromises. You have to be honest with yourself about that."

Moreover, it is for individuals – and families – to work out what is right for them: "There's not a template to follow. Everybody has to decide what works for them." In her case, her husband took a step back from his career: "Without him doing that, there was no way I could have taken on those extra leadership roles," she suggests.

Professor Tracey questions whether the notion of 'work–life' balance truly applies in science: "It's a privilege to be able to do what we do. I don't see it as thing I have to counterweight life against." Rather, she sees all the things she does, including 'work', as part of a mosaic or composite: "I have this mix of things I enjoy doing, and at different points in one's life this composite changes."

She has also reluctantly come to realise that being a woman in a leadership position does matter. Sex may seem an irrelevance when your aim is just to do a job as best you can, but seeing successful women can be inspiring and establish new norms: "It doesn't take many to change the culture and to change the optics and to raise the bar of expectations so that women automatically assume 'well, of course I could go and become that because x, y and z did it'. And that does make a difference."

Moreover, she emphasises how her husband's actions have also been influential: "This isn't just about women, it's also about men standing up and doing things like my husband did. It sent a very good message to his junior colleagues, who similarly followed suit."

Running for pleasure (and charity).

In the autumn of 2019, Professor Tracey took up a new challenge, as Warden of Merton College – her *alma mater*. "The reason I'm doing it is because this is where I came as an undergraduate and I stayed on as a graduate. Because it was just so transformative for me, I want to give something back to somewhere that was incredibly important in my life."

Again, timing was key: if she hadn't taken up the appointment in 2019 when a vacancy became available, it would be at least seven more years before the chance would have come again. It was a big leap – she resigned a prestigious university chair to take up a temporary appointment. So far she has no regrets and is loving the new role and, importantly, is being given the time to continue her research.

Again, she is not worried or looking to far-out horizons: "This is what I want to do now for this next phase. Who knows what I'll do afterwards, if anything – the one thing I have learnt is that opportunities unexpectedly arise, so I'm just going to see this bit through and do the best I can and see what comes up."

Q&A: Pia Siegele

Pia Siegele (Edinburgh) was the winner of the BNA's Undergraduate Award 2019.

Q: What did you discover in your research?

As part of my application for the BNA undergraduate prize, I submitted two pieces of research. One was my honours dissertation in which I used whole-cell patch-clamp recordings to investigate the connectivity of neurons within layers 2b and 3 in the lateral entorhinal cortex (LEC), a brain region important for episodic memory. My data provided new evidence that the outputs and projection patterns of the two layers are not only distinct from each other but also differ from corresponding layers of the adjacent medial entorhinal cortex. Such morphological studies will hopefully help us better understand the structure of the LEC's neuronal circuitry and the computations carried out within it.

The second project I submitted was a pathway diagram which aimed to integrate current knowledge on microglial signalling pathways relevant to Alzheimer's disease. My diagram highlights the interconnectivity of these pathways and how important it is to consider this interconnectivity when trying to understand the disease and develop effective treatments.

Q: What did you think when you heard you'd won the BNA award?

I felt very honoured to have been awarded the BNA undergraduate prize!

Q: What are you doing now?

I am currently doing a Master's in Cognitive Science within the School of Informatics at the University of Edinburgh. Throughout my postgraduate studies, I hope to acquire valuable advanced computational and mathematical skills to complement my expertise in neuroscience. I am hoping to do my master's project on a topic that involves interactions within neuronal networks.

Q: What are your long-term plans?

I haven't made up my mind yet on what to do after I finish my master's in August 2020 – there are so many interesting and exciting possibilities! Wherever I end up, I hope to make valuable contributions to our scientific community in the future.

Annette Dolphin presents Pia Siegele with her award.

Q: What do you enjoy doing outside science and medicine?

I enjoy travelling, swimming, skiing and hiking in my free time. When I am at home in Germany, I enjoy going on long walks with my Icelandic sheepdog. I also very much appreciate good food and like to cook dishes from all over the world.

Q&A: James Phillips

James Phillips (Cambridge) was the winner of the BNA's Postgraduate Award 2019.

Annette Dolphin presents James Phillips with his award.

Q: What did you discover in your research?

I did a few projects, but they centred on how different brain areas interact. In one, I started a project called thalamoSeq, which sought to understand the organisation of the central communication hub of the brain, the thalamus, using genetic sequencing of its projections. We discovered that there are deep similarities in the organisational patterns of the pathways that get to visual, motor, prefrontal and other cortical areas from the thalamus. This provides support to the notion of a relatively 'universal' function algorithm in thalamic systems, an architecture on which specialisations can then arise for each system.

Q: What did you think when you heard you'd won the BNA award?

I had to read the letter three times because it was surprising! But I felt very happy. It came right after I preprinted a paper from my thesis that the team had just finished, so it came at a good time.

Q: What are you doing now?

I'm currently teaching myself some mathematics and theory to prepare for a postdoc, and am also finishing a book I have been writing since the start of my thesis. It is kind of a neuroscience book, but also a bit broader than that, combining some other areas of science/philosophy.

Q: What are your long-term plans?

Fingers crossed to work as a researcher at the interface of theory and experiment, studying brains. The main next step is to get the skillset needed to do a project with a higher theoretical/modelling component – I've mainly done analysis and experiments so far so it's a gap to fill.

Q: What do you enjoy doing outside science and medicine?

I enjoy watching cricket, and also writing (see above) and reading. But discussing, researching and then putting into action ideas/hypotheses is my main passion – science for me is a very social endeavour and discussing it with others is not just important, but a central part of refining ideas and hypotheses.

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