Bright Brains Newsletter

Issue No. 7
Autumn 2017

Welcome to the third autumn edition of our 'Bright Brains' Newsletter! In this edition we are excited to welcome you to the final part of the three-part series, in which the last page of 'Varietas' is dedicated to the exploration of the mind and the brain from an artistic perspective. While the previous two editions covered the visual arts and poetry as means by which neuroscientific phenomena and ideas can be creatively expressed, this edition adds a musical touch to the contemplation of the mind and the brain.

While previous research on the effect of music on intelligence has debunked the myth of the 'Mozart effect', which first surfaced in a *Nature* report in 1993 that claimed listening to Mozart for 10 minutes enhanced participants' performance on spatial tasks, recent evidence suggests there is an effect of music training on IQ in developing brains. According to a study at the Northwestern University in Chicago, learning to play music helps children toward the development of a neurophysiological distinction between certain sounds, which can help them with their literacy. Active engagement and participation in creating music, specifically, predicted neural processing strength after music lessons. Moreover, when coupled with consistency in attending music training, active class participation was revealed to lead to enhanced effects on speech processing and reading scores.

As an adult, could you still expect to see any benefits if you take up a musical instrument late in life? Luckily, the answer is yes! A study at the University of South Florida that looked into the impact of piano training on adults aged between 60 and 85 demonstrated how, after 6 months of piano training, recipients of lessons improved in verbal fluency, planning, memory and pace at which information is processed compared to those who did not have piano lessons. Thus, no matter if you have never played an instrument, or have not played music in decades, 'Bright Brains' would like to help you stimulate your brain in creative ways by encouraging you to pick up your musical instrument and arm yourself against cognitive decline and memory loss. Benefits are plenty, so what are you waiting for?

Apart from facilitating the process of learning to read, music does more than just impact on our cognitive development: it taps into our inner selves, allowing us to express the inexpressible. Where words alone are insufficient, music speaks to our hearts. As the Lebanese poet Kahlil Gibran once stated: "Music is the language of the spirit. It opens the secret of life, bringing peace, abolishing strife." I can relate to this view with my first-hand experience of having performed *Veena* music at the opening ceremony of the Transnational Government of Tamil Eelam night for the United Nations at Wembley earlier this year, where music set the scene for fruitful discussions on how to bring about justice for war victims and end genocide.

Moreover, this special 'Bright Brains' autumn edition has many great features in store for you: the 'Nuntia' section reviews the International Neuroinformatics Coordinating Facility (INCF) nodes workshop that took place in Oslo, and provides you with a report on the XIII European Meeting on Glial Cells in Health and Disease. Our 'Socialia' section presents a student perspective on the Neonatal Connectome Course that took place in Utrecht, and draws your attention to a new online initiative to support open science. Our 'Varietas' section assesses a new technology that visualises the three-dimensional structure of neurons, and proposes that clinical trials should always consider the participation of pregnant women. Also, 'Varietas' investigates how stem cells could be used to heal spinal cord injury, and introduces you to a new online neurosurgical education initiative called 'Brainbook'. Last but not least, we are challenging you to have a go at our BNA crossword, which has music as its theme.

Finally, we sincerely hope that you will have as much joy reading our 'Bright Brains' newsletter as we had in producing it. On that note, we would like to encourage you to get involved in science communication by joining our newsletter team. Please direct enquiries to jayanthinykangatharan@gmail.com.

Jayanthiny Kangatharan, 'Bright Brains' newsletter coordinator

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International Neuroinformatics Coordinating Facility (INCF) nodes workshop

"If the human brain were so simple that we could understand it, we would be so simple that we couldn't."

These are the words of engineer and scientist Emerson Pugh (1). Indeed, the specificity of connections, the structure of cells and synapses, and the intricate molecular and physiological basis of the brain's operations make it overwhelmingly complex. Although this is partly the reason why we still lack a deeper understanding of the brain, neuroscientists also face the significant challenge of making sense of exponentially increasing amounts of data.

The International Neuroinformatics Coordinating Facility (INCF; **incf.org**) develops and promotes standards, tools and infrastructure for neuroscience researchers. In May 2017, INCF held its 16th nodes workshop in Oslo, Norway.

The workshop began with talks on tools for teaching neurophysiology and neuroanatomy. A tool for simulation and interaction with neuronal networks (2) was demonstrated, and novel neuroanatomy resources (3,4) were introduced. Interesting tools for integration of neuroscience data were presented the next day, including interactive brain libraries, three-dimensional rodent (4) and human (5) atlases, and software for histology-based atlasing and machine learning-based image analysis (6). Maryann Martone closed the session by encouraging findable, accessible, interoperable and re-usable (FAIR) research (7) for humans and machines.

As an early-career scientist starting out in neuroinformatics, I was humbled (and frankly a little star-struck) by being surrounded by experts in the field, and inspired by the opportunity to discuss ideas with these people. I encourage anyone looking to do reproducible and re-usable neuroscience to get involved in the INCF community. If we aspire to make our research FAIR, we may one day prove Pugh wrong and gain a true understanding of nature's most complex structure: our own brain.

1. **Pugh GE** (1977) *The biological origin of human values*. New York: Basic books.
2. **Dragly SA *et al*.** (2017) Neuronify: An educational simulator for neural circuits. *eNeuro*. 4(2) ENEURO.0022-17
3. **Rodent Brain Workbench**. Available at http://www.rbwb.org/ [Accessed 1 June 2017]
4. **Waxholm Space Atlas of the Sprague-Dawley Rat Brain**. Available at https://www.nitrc.org/projects/whs-sd-atlas [Accessed 1 June 2017]
5. **BigBrain**. Available at https://bigbrain.loris.ca/main.php [Accessed 1 June 2017]
6. **Kreshuk A *et al.*** (2014) Automated detection of synapses in serial section transmission electron microscopy image stacks. *PLoS ONE* 9(2): e87351
7. **Wilkinson MD *et al.*** (2016) The FAIR guiding principles for scientific data management and stewardship. *Sci. Data* 2016 (3):160018.

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Euroglia 2017 – XIII European Meeting on Glial Cells in Health and Disease

A good conference is one that inspires new ideas, questions, connections, job opportunities and, most importantly, enthusiasm for science. My experience at Euroglia satisfied all these requirements and many more. More than 1000 scientists gathered in Edinburgh on 8–11 July 2017 for plenty of discussion over seven plenaries, 30 symposia, two workshops, one introductory course and 767 posters.

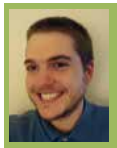
In particular, the introductory session on glial biology deserves to be highlighted. It aimed to teach early-career researchers about the cutting-edge techniques such as *in vivo* and super-resolution microscopy, CRISPR7/cas9 systems, and chimeric mouse models. In addition, it provided an excellent opportunity to ask questions about glia biology. This was especially useful for those who are glial biologists in training. Indeed, the introductory session's chair greatly encouraged questions from the audience, setting the tone for the rest of the conference, with symposia chairs placing a strong emphasis on stimulating productive Q&A sessions. This created a very collegiate atmosphere, and led to thought-provoking conversations that continued at the conference ceilidh.

The scientific programme was very well organised, covering an excellent variety of topics from glial development in *Drosophila* to microglial transcriptomics from post-mortem human tissue samples. I found it particularly interesting how crucial the provision of cholesterol by glia is to the development and maintenance of the synapse. The programme saw a great diversity in both topics and invited speakers, with many of the speakers being young principal investigators. A good gender balance was also noticeable at both the symposia and plenary lectures.

Euroglia meeting welcome.

Early-career researchers strongly rely on posters to showcase their research, establish new collaborations and receive useful feedback. Thus, despite the challenging navigation and the slightly confusing poster numbering system, it was impressive to find the poster area so busy, with early-career scientists exploring fascinating research and networking with other academics. I feel it was definitely one of the most interesting meetings I have been to.

I greatly enjoyed my time at Euroglia – it was inspiring, and welcoming to scientists at all stages of their careers. I look forward to the next meeting.



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Connecting through Neonatal Connectome Course – A student perspective

Who says summer camp isn't for adults? As a group of students from the University of Edinburgh, we were lucky enough to attend the Current Issues in the Neonatal Connectome course at the University Medical Centre (UMC), Utrecht, The Netherlands, on 12–16 June 2017. It was a remarkable week filled with engaging conversations, a constant feeling of being inspired by scientific advances, and the joy of experiencing the local culture in Utrecht.

Each morning, the course featured four different talks from scientists and clinicians around the world as a platform to discuss one of the most vulnerable populations on Earth: infants. After each talk, open discussion was encouraged between speakers and attendees. When asked about our favourite parts of these discussions, here were some of the answers:

"One of the most remarkable aspects … was the ability for [the course] to cover the link between the technical and clinical world[s]." – Manuel Blesa Cábez

"… I am very excited to see the results from the forthcoming trial of stem cell therapy for treatment of neonatal stroke, and loved learning more on fetal MRI imaging from the keynote speaker, Dr Moriah Thomason." – Gemma Sullivan

In addition to the speakers, there were several options for two-day workshops organised as 2–3-hour afternoon sessions. These workshops offered a deeper insight into the technical methodology underlying both the work presented in the morning talks and general connectome research.

Another highlight was the collaboration between the University of Edinburgh and the UMC hosts to coordinate one-on-one lab visits for students. Prior to attending, students were asked to name UMC faculty who they would like to visit. The willingness of the UMC faculty to participate in these small, intimate conversations reflects the networking and collaborative emphasis of the week.In addition, on the first day students were divided into groups and asked to develop a 5–10-minute mock-up proposal on a topic of their choice, to be presented on the final conference day. Inspiration from the week's talks shone through the pitches, with many groups incorporating themes featured in the course.

Overall, the UMC course provided a unique opportunity to learn and develop new skills, and to connect over shared interests. These shared interests are an important foundation for promoting creative thinking beyond the simple labels commonly attached to ourselves and our work – scientist; psychologist; clinician; radiographer; engineer. That truly was the highlight of the week, and something that will not be easily forgotten.

Alexander Morley
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Networked communities – building the cultural and educational resources required for a successful transition to open science

The tools many of us use on a daily basis would have barely been imaginable this time last century. But the ways in which we report our findings and judge our peers have barely changed at all. Driven by concerns over reproducibility, as well as by a plethora of technological advances such as the widespread availability of the internet, best research practices are rapidly being remoulded. While these changes, reflected in a movement often referred to as 'open science', are increasingly being included in research evaluation frameworks, many universities are failing to provide the training or incentives that would enable young researchers to keep pace.

Fortunately, in many online spaces and non-traditional organisations, opportunities for training and networking are flourishing. My introduction to open science involved stumbling across the Mozilla Science Lab's website (**www.science.mozilla.org**) a few years ago. This organisation supports open science advocates through fellowships, mentorship and project-based learning. For me, the key to its influence in this sphere so far has been its success in facilitating truly inclusive and diverse online communities.

The benefits of such networked communities are apparent even for developing skills in the classroom. Software Carpentry (**www.software-carpentry.org**) has grown from a few frustrated computer scientists trying to teach engineers how to parallelise their programs to a global organisation running intensive two-day workshops for tens of thousands of scientists every year. The development of teaching materials in an open and collaborative environment has led to their continuous refinement by a diverse community. Its impact is visible in lessons that have been altered to fit within an evidence-based educational psychology framework. Too many curricula are created without the recognition of how much research has been done on how people learn!

While the Mozilla Science Lab, Software Carpentry, and a multitude of other online resources and communities continue to support scientists' educational needs, as of yet, there is no one-stop shop for learning about open science. In a massive collaborative project led by palaeontologist Jon Tennant, we are proposing the development of a new open science massive open online course (MOOC; **www.goo.gl/WP9WBw**), which will be designed to equip researchers with those skills that are needed to excel in a modern research setting. It aims to foster students' agency over their self-representation and identity on the web, and to enhance individuals' ability to collaborate openly. Both these skills are crucial for the participation of future scientists in a global research environment.

Jack Cooper
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Imaging with CLARITY

Santiago Ramon y Cajal, viewed by many as the father of neuroscience, once said that the brain includes "a number of unexplored continents and great stretches of unknown territory". One of the major barriers to better mapping these continents is the opaque nature of the brain. Single-photon and two-photon microscopy can only image as deep as 50 µm and 800 µm below the brain surface, respectively, preventing complete visualisation of global neural projection patterns and cell population positions. Instead, many thin brain slices have to be imaged and then reconstructed into three-dimensional structures later – both time-consuming and costly. That is until the development of CLARITY (clear lipid-exchanged anatomically rigid imaging/immunostaining-compatible tissue hydrogel), a Stanford-developed technology resulting in transparent brain tissue.

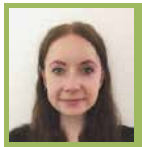
Following the injection of both formaldehyde, used to fix the tissue, and hydrogels, the CLARITY process then heats the brain and removes fats via chemical or electrical means. This leaves a transparent tissue–hydrogel mesh that retains the tissue's original three-dimensional structure (1), while endogenous biomolecules such as neurotransmitters, proteins and nucleic acids are fixed in place.

By visualising this three-dimensional structure of neurons, as well as the expression and localisation of mRNA, proteins and neurotransmitters in the context of those structures, CLARITY allows us to extend our understanding of brains in normal and disease states. The treated tissue is both permeable to large molecules and hardy enough to be washed; this enables multiple rounds of antibody labelling of proteins and *in situ* hybridisation of nucleic acids. Unlike traditional approaches, this technique generates a high volume of information about local morphology, such as synapse type, and global morphology, which is incredibly powerful for understanding network dynamics.

Since its inception, CLARITY has been used to characterise many disease pathologies in three dimensions, including those involved with Alzheimer's disease (2), multiple sclerosis and anxiety disorders, and is even being evaluated for applications in cancer and autoimmune disease diagnosis. CLARITY also helps us better understand development, and the three-dimensional movements and interactions of cells in the embryo.

Despite disadvantages including the large start-up costs involved and the time taken for the clearing process to run and for the immunostaining of thick tissue, CLARITY is an exciting technological advancement towards understanding and relating brain circuit activity across multiple areas, thus holding great promise in helping us see through the mysteries of the brain.

1. **Chung K *et al.*** (2013) Structural and molecular interrogation of intact biological systems. *Nature* 497(7449): 332–337.
2. **Ando K *et al.*** (2014) Inside Alzheimer brain with CLARITY: senile plaques, neurofibrillary tangles and axons in 3-D. *Acta Neuropathol* 128 (3): 457–459.



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Pregnancy in clinical trials: not vulnerable, but complex

The relevance of human clinical research in establishing safe and effective medical therapies is well recognised. However, other than research on pregnancy itself, there is a dearth of trials specifically addressing questions pertinent to pregnant women. This results in doctors relying on inferences from drug studies that have explicitly excluded pregnant women. While pregnant women suffer from the same medical conditions as the general population, they experience substantial physiological changes during gravidity, and these are likely to impact on pharmacodynamics. Extrapolation from such studies is, therefore, a flawed way of informing pharmacological dosage, and doing so means pregnant women are in danger of under- or mis-treatment, and are ill-informed about the risks that exposure to therapies could pose to themselves and their unborn child. The need for a more informed understanding of therapies during pregnancy is compelling and this can only be achieved by involving this population in clinical research.

Of course, many apposite restrictions to the inclusion of pregnant women in research exist, and there cannot be a universal answer regarding their involvement since not all clinical experiments are alike. However, one barrier that needs addressing, and is the reason for much of the widespread reluctance to include pregnant women in research, is their historical classification as 'vulnerable'. While caution in involving pregnant women in research is of course appropriate, and no one would challenge the importance of preventing avoidable harm to women and their fetuses, it seems there should be an attempt, both scientifically and ethically, to reclassify them as 'complex' rather than 'vulnerable', when considering their participation in clinical trials. Research involving a complex cohort would have its own unique challenges and would need a clear ethical framework, but with thoughtful study design, and after initial safety and efficacy profiles have been established elsewhere, risks can be minimised and great benefits can be achieved.

Results from such trials are crucial for achieving the effective management of conditions concomitant with pregnancy and for superseding the existing standard of care. Pregnant women, like all other members of society, need safe, effective, evidence-based treatments, which can only be achieved by involving them in clinical research. In doing so, we can move away from protecting pregnant women and their fetuses from research, to protecting them through research.

This article is an extract of a more detailed discussion, which can be found at: **www.bna.org.uk/publications/bright-brains/bb-online/**

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Fixing the unfixable: could stem cells be the answer to curing spinal cord injury?

Every year 300,000 people, mostly between the ages of 20 and 29, are diagnosed with a spinal cord injury (SCI). Such damage occurs when any number of the 13.5 billion neurons that make up the spinal cord die. Patients with SCI suffer a variable degree of functional loss to a particular muscle group, depending on the site and extent of injury. Unsurprisingly, these kinds of injury are associated with a range of sociological and economic effects, with 60% of patients being unemployed and 20–30% suffering from depression. This adds to the urgency to find a cure (1).

Over the past 20 years, many researchers have turned to mesenchymal stem cells (MSCs) as a possible treatment for SCI. MSCs are extracted from bone marrow and have the potential to differentiate into cells that make up bone, cartilage or fat. However, under the appropriate conditions, MSCs can also develop along neuronal lineages, making them a promising potential therapeutic treatment for replacing cells that are lost or damaged in SCI.

MSCs are favoured over stem cells of other lineages as they are anti-apoptotic, anti-inflammatory and anti-tumorigenic by nature. Trials are currently underway to investigate the viability of MSCs as an effective treatment. However, results to date have been mixed and researchers are also looking into alternative approaches.

For example, cell therapies for SCI might be more effective if they were based on transplantation of neuronal cells rather than undifferentiated stem cells. To this end, researchers have been developing methods to generate neuronal cells from pluripotent stem cells, such as embryonic stem cells or induced pluripotent stem cells (adult cells that have been converted into pluripotent stem cells). For example, a US–China collaboration have described a highly efficient method for generating motor neurons (2), while US researchers recently described a method for generating V2a interneurons and showed that they could integrate into the spinal cords of mice (3).

Although many hurdles remain, these types of studies could one day provide a much-needed source of cells for treatment of SCI.

1. **World Health Organisation** (2013) Spinal cord injury. Available at www.who.int/mediacentre/factsheets/fs384/en/ [Accessed 7 May 2017]
2. **Qu Q *et al.*** (2016) High-efficiency motor neuron differentiation from human pluripotent stem cells and the function of Islet-1. *Nat. Commun.* 5:3449
3. **Butts JC *et al.*** (2017) Differentiation of V2a interneurons from human pluripotent stem cells. *Proc Natl Acad Sci USA* 114(19):4969–74.



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Academic Foundation Doctor and Brainbook Co-Founder
Alex Alamri
Neurosurgery Registrar and Brainbook Co-Founder, Royal London Hospital

Brainbook

The psychosocial impact on patient groups is little discussed in neurosurgical and healthcare circles despite a good understanding of how significant this is to patient care. With that in mind, we created Brainbook: a multimedia and multiplatform encyclopaedia of neurosurgery, which focuses on patients first including vital communication skills that patient care entails, leadership skills that neurosurgeons require, and technicalities that are involved in neurosurgery and neuroanatomy. Our website (**www.realbrainbook.co.uk**) contains blog posts, split into three separate sections:
1. For patients and the public
2. For medical students, neuroscientists and allied healthcare professionals
3. For neurosurgeons.

Blog posts may be written by anyone and can be aimed at any of the above groups. Examples include posts by neurosurgeons writing for neurosurgeons (regarding technical skills, literature etc.) or for patients. Contents can range from what a neurosurgeon's life is like to what neurosurgeons find most difficult about caring for critically unwell patients. The website also features videos of surgical operations using GoPro footage from a camera mounted on the surgeon's head. This gives a surgeon's eye view.
We aim to post video experiences of all the major neurosurgical emergencies and elective operations on the Brainbook website.

We created pilot videos that followed real patient stories, which were discussed on social media primarily with junior doctors and other healthcare professionals. Members of the public were also encouraged to join us and ask questions.

We are now moving towards creating technical videos for neurosurgeons and more stylised (but realistic) videos for other healthcare professionals and the public so that they might better understand what occurs during surgical operations. Physiotherapists and speech and language therapists at the Royal London Hospital, for example, have found it useful to see exactly what patients undergo during surgery and they feel that it helps them to better assess and rehabilitate patients.

We know that the neurosciences are a foundation of what neurosurgeons can achieve in the operating room. We therefore welcome blog articles from BNA members as well as collaborations. We are looking forward to hearing from you – you can contact us at **alex@realbrainbook.co.uk**.

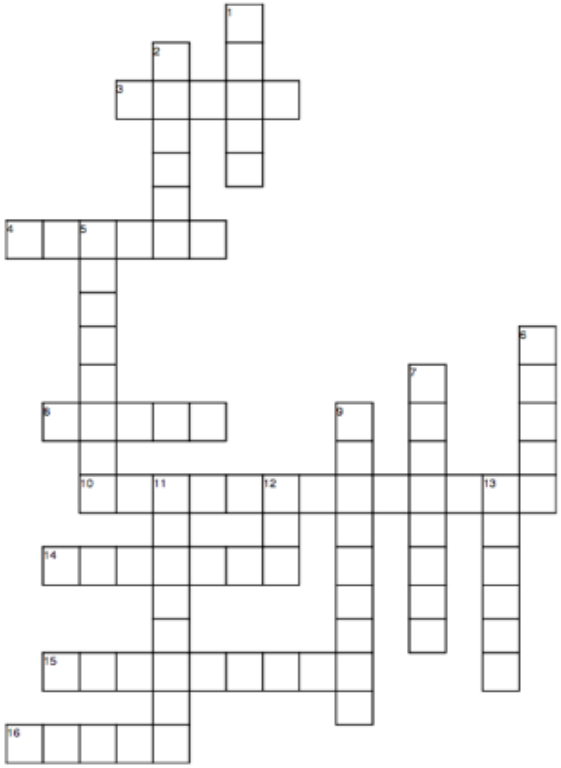
How well does your brain appreciate music?

Test your knowledge by completing the following simple crossword. Answers will be revealed in the next edition. Answers to last edition's visual riddles are provided at the bottom of the page.

Enter this edition's competition by sending your answers to **jayanthinykangatharan@gmail.com**. Entries received before 1 February 2018 will be entered into a prize draw to win a unique contribution towards the 'Bright Brains' spring edition!

Across
3. An instrument of the violin family, larger than the violin and tuned lower.
4. The 'stirrup-shaped' bone of the middle ear.
8. A traditional form of Japanese poetry, typically evoking the natural world.
10. Two words: The ability to identify or produce a musical tone at a given pitch without using an external reference pitch.
14. Latin for snail shell. Involved in auditory processing.
15. Two words: Poetry that does not rhyme or have a regular rhythm.
16. The number of notes in an octave.

Down
1. Composer of *The Planets*
2. The quality that distinguishes two sounds equal in pitch, loudness, spatial location, and duration.
5. The centre of emotional processing in the brain.
6. The percept relating to the periodicity of a sound.
7. The lobe of the brain that processes the rhythm of music.
9. German composer who became deaf.
11. This Viennese-born composer died aged 31, probably of syphilis.
12. The country with the largest music industry market
13. Percept relating to the wavelength of light



Answers to the visual riddles from Issue 6 – Summer 2017 – 1: Cerebellum; 2: hippocampus; 3: hypothalamus; 4: pineal gland; 5: basal ganglia; 6: pons; 7: astrocyte; 8: brain stem.