Issue No. 93
Autumn 2021

BNA Bulletin

THE VOICE OF BRITISH NEUROSCIENCE TODAY

A deep dive

Brain imaging in seals

Biology's hydrogen atom

Worm brains and behaviour

PLUS:

Multi-omics in Alzheimer's disease

COVID-19 and the brain

Ratlas unveiled

BNA
British Neuroscience Association

FENS Forum 2022

9-13 July 2022 | Paris, France

SAVE THE DATE

1 December 2021 - 22 February 2022: call for early registration, abstract submission and FENS-IBRO/PERC travel grants

Discover the preliminary programme online!

FENS Federation of European Neuroscience Societies

Société des Neurosciences

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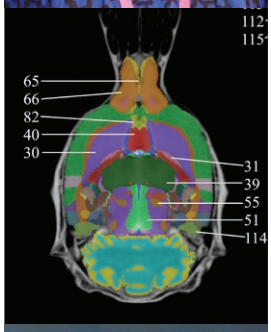

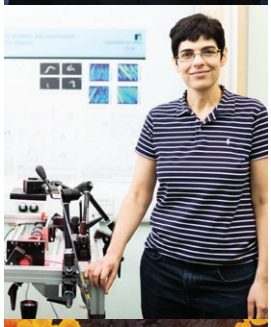

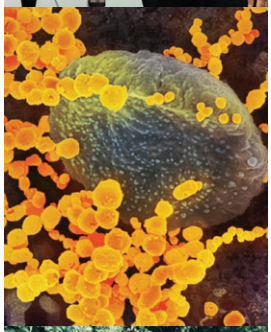

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Seals are expert divers, and capable of remarkable control over their autonomic nervous systems. See page 26. Image: Joseph Skinner/ WikiMedia Commons.

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Message from the President and Chief Executive

Dear BNA Members

At the time of writing, we're not sure what this autumn term of the academic year will bring. We certainly hope it will be less challenging and more sociable for you – whether you're a student, working in pharma or medtech, a researcher or a lecturer – than last year's.

It's been a busy summer at the BNA as we prepare activities for the coming year. In particular, having received an overwhelmingly positive response to launching an **online 'Members' Meeting'** in non-Festival years (94% of 124 respondents thought it was an 'excellent' or 'good' idea), we are now busy making plans for this to happen. Thank you for your feedback! You made important suggestions, and we will try to accommodate as many as possible. Based on ideas so far, the plans are for this meeting to:

1. Be by members, for members
2. Take place over two short days, during core working hours (10am–3pm)
3. Feature short talks with plenty of chance for discussion
4. Prioritise postgraduate and early-career researchers
5. Especially encourage talks about planned as well as completed work, to foster discussion and provide most benefit from feedback from colleagues.

We will not have posters, since our experience is that these do not work well online, and there will be plenty of in-person opportunities at the FENS Forum (Paris, 9–13 July 2022) as well as future BNA Festivals.

Check out details on the BNA website, and look out for the call for talks. Because of the limited number of slots, talks will generally be accepted on a first-come first-served basis, with the proviso that we will try to minimise talks from the same institution and maximise the diversity of speakers. We will try to group talks into themes for each session, and there will be a few special talks from the BNA's annual prize-winners. We will also look into a networking/speed-dating component. Until then, please make a note in your diaries for **27–28 April 2022, for our first Members' Meeting!**

Finally, a reminder that our annual theme for 2022 is 'Artificial Intelligence and Neuroscience', which will be launched at our Festive Symposium on 13 December 2021, entitled 'Ding dong merrily on AI: What artificial intelligence can tell us about biological intelligence'. This will be online again this year, and we hope to see you then!

Rik Henson
BNA President

Anne Cooke
BNA CEO

Festive Symposium

The much-loved BNA Festive Symposium – 'Ding dong merrily on AI: What artificial intelligence can tell us about biological intelligence' – will take place virtually on 13 December 2021. As usual, the Symposium will introduce next year's BNA theme, artificial intelligence and neuroscience. See **bit.ly/3AgCKD4** for further details.

Members' Meeting

By popular demand, the BNA is launching a brand new type of event: 'Members' Meetings' will be online, held in non-Festival years, and emphasise sharing and discussion. See you on 27–28 April 2022!

BNA*2021*

Many of the highlights of BNA*2021*: Festival of Neuroscience are now freely available to all. Plenary lectures and a range of special sessions – including those on green neuroscience, equity, diversity and inclusion, and credibility – can now be viewed at **bit.ly/3ac4Kgr**.

Webinars

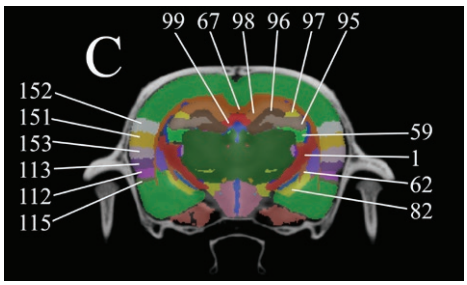
The BNA has joined forces with the Psychiatry Consortium to organise a series of free webinars highlighting the importance of collaboration between industry, academics and patient groups in psychiatric drug discovery. The five-part series, 'Building bridges along the psychiatric drug discovery pipeline', will span all stages of drug development, including identifying unmet medical needs, understanding disease mechanisms and developing novel treatments. The webinars will run from November 2021 to March 2022. See **bit.ly/3FiEcZ8** for registration details.

AGM minutes

The BNA AGM took place on 21 June 2021. Minutes, the Trustees' Annual Report for 2020 and BNA accounts can be accessed at **bit.ly/38Cp6yD**.

Ratlas arises

Brain and Neuroscience Advances has published a freely available atlas of the rat brain, colloquially known as 'Ratlas'. Developed by researchers at Nottingham and Magdeburg, Germany, Ratlas will be an invaluable resource for researchers working on a critical model organism in neuroscience. See page 14 for more details.



Carer grants

The BNA has launched a BNA–Brain Carer Grants scheme, to help cover expenses associated with caring responsibilities and enable participation in either BNA-hosted or external neuroscience events.

Previously awarded to carers attending our Festivals of Neuroscience, BNA–Brain Carer Grants have been positively received by the neuroscience community for acknowledging caring responsibilities, which can make it hard for neuroscientists to participate fully in events such as conferences.

The **Guarantors of Brain** have now extended their support beyond the Festivals, so that BNA–Brain Carer Grants of up to £200 can be offered to neuroscientists with children or other caring responsibilities. Further details can be found at **bit.ly/3tYz0oa**.

BNA scholars

The application process for 2022 BNA Scholars has opened. The BNA Scholars programme provides support to students from underrepresented ethnic groups, enabling them to thrive in neuroscience and build a supportive community through networking opportunities, bursaries, and mentorship. It also offers students membership of the BNA and FENS, as well as funding towards conferences. The programme is open to final-year undergraduate, master's or PhD students, as well as research assistants and technicians, who self-identify as Black, Asian or minority ethnic.

In September 2021, **Hello Bio** announced its support for the Scholars Programme 2022, by providing a £300 bursary for each student to support them with their scientific career.

See **bit.ly/3u1o1Kz** for more details of the programme and how to apply.

Dementia in Scotland

The BNA has endorsed the first Scottish Brain Health and Dementia Research Strategy, designed to boost care and prevention research for dementia in Scotland. The strategy, developed by Alzheimer Scotland, the Scottish Dementia Research Consortium and Brain Health Scotland, identifies key areas of research in brain health and dementia for Scotland. The new strategy can be viewed at **bit.ly/3kQy29l**.

FENS Forum

The countdown has begun to FENS Forum

2022, due to be held in Paris, France, on 9–13 July 2022. Plenary lectures will be delivered by, among others, **Irene Miguel-Aliaga** (Imperial) and **Matteo Carandini** (UCL), and special lectures will be given by **Peter Goadsby** (KCL), **Tim Behrens** (Oxford/UCL) and many other notable figures from Europe, the USA and elsewhere. Registration will open on 1 December 2021.

In addition, a call is now open for satellite/networking events associated with the Forum. See **https://forum.fens.org/networking-events/** for details of how to organise an event.

STEM equity

Earlier this year, the BNA submitted evidence to the All-Party Parliamentary Group (APPG) on Diversity and Inclusion in Science, Technology, Engineering, and Mathematics (STEM), whose report into 'Equity in the STEM workforce' was published in July 2021. The report takes into account evidence from more than 150 individuals and organisations, and makes three recommendations for the UK Government and the STEM sector, including development of a 'STEM Diversity Decade of Action'. The report can be downloaded at **bit.ly/3lQ1kVZ**.

Neurotech

A new report has outlined the steps the UK needs to take to become a world leader in neurotechnology. The report, 'A transformative roadmap for neurotechnology in the UK', has been produced by the Knowledge Transfer Network, established by Innovate UK to link public and private sectors to boost global innovation. It highlights the exciting potential of applying engineering principles to our understanding of the human brain and nervous system, through innovations such as brain–computer interfaces, while also identifying barriers currently preventing this area of research from being translated. The report calls for the creation of a **Neurotechnology Accelerator**, to provide a test bed for device developers. The report can be downloaded at **bit.ly/3zHHWR5**.

Open research

The UK Reproducibility Network, a consortium of 18 UK universities of which the BNA is a founding affiliated stakeholder, has been awarded £8.5m, including £4.5m from the Research England Development fund, to promote uptake of open research practices. The funding will support a programme of training and impact evaluation. The programme is being led by **Marcus Munafo** (Bristol).

Neuroscience day

The 2021 Edinburgh Neuroscience Day was held on 23 September 2021, as a hybrid event with physical and virtual participants. The Annual Distinguished Lecture 2021 was delivered by **Masud Husain** (Oxford). The meeting included sessions devoted to postdocs and fellows, a student data blitz, and presentations by **Jasna Martinovic**, **Suvankar Pal**, **Nikki Robertson**, **Crispin Jordan**, **Gillian Currie** and **Danny Smith**.

Neuroscience in Wales

The Royal College of Psychiatrists' Wales Neuroscience Conference was held on 8 June 2021 via Zoom. Speakers included **Kim Kendall** (Cardiff), **Seth Mensah** (Welsh Neuropsychiatry Service), **Claire Hanley** (Swansea), **Jeremy Hall** (Cardiff), **Jack Underwood** (RCPsych Neuroscience Champion for Wales), **Kami Kaldewyn** (Bangor) and **Mara Cercignani** (Cardiff). The meeting formed part of the RCPsych's Neuroscience Project, which aims to strengthen connections between psychiatric practice and neuroscience research in the UK.

Steve McMahon


Steve McMahon

The BNA was deeply saddened to hear of the death of **Steve McMahon**, one of the UK's leading pain researchers, in October 2021. Professor McMahon was Sherrington Professor of Physiology at KCL, a Wellcome Senior Investigator and head on the Wellcome Trust Pain Consortium. In 2019, he was awarded the BNA's Outstanding Contribution to Neuroscience Award.

Epilepsy PhDs

Cathy Abbot and **Richard Chin** (Edinburgh) have been awarded £250,000 from Epilepsy Research UK (with matching funding from the University of Edinburgh) to establish a new doctoral training centre focused on 'Improving outcomes for childhood onset epilepsies: from mechanisms to treatment'. The centre will bring together experts in basic science and clinical skills to lead PhD research projects to provide insights into how seizures occur and improve methods of diagnosis, while preparing researchers for a career in epilepsy research.

GW4 training

The GW4 Alliance – comprising the Universities of Bath, Bristol, Cardiff and Exeter – has been awarded MRC funding for a doctoral training partnership (DTP) that will support 16 PhD studentships per year for three years, with each GW4 institution contributing an additional studentship each year. Led by **Colin Dayan** (Cardiff), the DTP focuses on three specific areas of medical sciences, including neuroscience and mental health.

The programme will focus on three cross-cutting strands: data science, interdisciplinary skills, and translation and innovation. It includes opportunities for students to broaden their horizons through industry placements, research visits, public engagement internships and personalised core skills training.

PD platform

The Edmond J Safra Foundation has awarded £1.4m to UCL and the University of Plymouth to establish an innovative platform for evaluating candidate drugs for Parkinson's disease. The adaptive 'multi-arm multi-stage' clinical trial platform will enable multiple drugs to be tested simultaneously and across different stages of clinical development, increasing the efficiency of drug testing.

The Accelerating Clinical Treatments for Parkinson's Disease project will be co-led by **Thomas Foltynie** and **Sonia Gandhi** (UCL) and **Camille Carroll** (Plymouth), in partnership with the Medical Research Council Clinical Trials Unit at UCL and leading Parkinson's disease researchers from across the UK, people living with Parkinson's and UK Parkinson's charities.

Second that emotion

An international consortium led from Bristol has received €4.5m from the European Research Council to explore the cerebellar brain circuits that underlie emotional behaviour.

A new virtual institute is being established under the Marie Skłodowska-Curie Innovative Training Network initiative. It will span seven European universities and nine industry/charity partners and support the training of 15 PhD students over the next four years.

The new consortium, CEN (Cerebellum and Emotional Networks), will be led by **Richard Apps** (Bristol) and also includes **Charlotte Lawrenson** (Bristol), **Peter Kind**, **Thomas Watson** and **Sally Till** (all Edinburgh). See **https://cenproject.blogs.bristol.ac.uk** for more details.

HD funding

A team of researchers from UCL, Cambridge and Glasgow, led by **Sarah Tabrizi** (UCL), has been awarded a £5.3m Wellcome Trust Collaborative Grant to take forward a programme of translational work on Huntington's disease. The research programme will explore molecular and cellular mechanisms of disease, potential interventions, and brain imaging of young carriers of the Huntington's gene.

AD funding

A team of researchers from Exeter, Bristol, Essex and the UK Dementia Research Institute at Imperial, led by **Jonathan Mill** (Exeter), has been awarded £1.5m MRC funding to explore patterns of gene activity in different cell types in the brain and their potential links to the development of Alzheimer's disease.

News in Brief

Nobel Prize

The BNA warmly congratulates **David Julius** (University of California San Francisco) and **Ardem Patapoutian** (Scripps Research), joint recipients of the 2021 Nobel Prize in Physiology or Medicine in recognition of their seminal research on receptors for temperature and touch.

Faraday Prize


Sophie Scott

Sophie Scott (UCL) has been awarded the Royal Society's Michael Faraday Prize and Lecture for her work in engaging the public with neuroscience through events, talks, TV and radio, and exemplifying how science communication can enhance scientific excellence.

ALBA

Laura Andreae (KCL) has been appointed Chair-Elect of the ALBA Network, an international initiative that promotes equity and diversity in brain sciences. Dr Andreae will become Chair of the ALBA Network in July 2022.

Lister Prize


Rickie Patani

Rickie Patani (UCL/Crick Institute) has been awarded a prestigious Lister Prize Fellowship for 2021. The £250,000 prize aims to support the work of outstanding early-career biomedical scientists. His research focuses on motor neuron disease and the use of stem cells from patients to better understand the disease and develop therapies.

EMBO

Congratulations to **Corinne Houart** and BNA*2021* plenary lecturer **Beatriz Rico** (KCL), who have been elected as new members of the European Molecular Biology Organisation (EMBO).

MS award

Alan Thompson (UCL) has received the 2021 Charcot Award, a Lifetime Achievement Award made by the MS International Federation (MSIF). The award recognises Professor Thompson's multiple contributions to research and treatment of multiple sclerosis over a 40-year career.

MRI award

Frederik Barkhof (UCL) has been awarded the International Society for Magnetic Resonance Imaging Gold Medal. Professor Barkhof has been recognised for his seminal contribution to the development of MRI technology and its application to the study and treatment of white matter disease and dementia.

PD award

K Ray Chaudhuri (KCL) has received the Honorary Membership Award from of the International Parkinson and Movement Disorders Society (MDS), which recognises persons who have made extraordinary contributions to the field of movement disorders. Professor Ray Chaudhuri's research focuses on Parkinson's disease, particularly non-motor symptoms.

Epilepsy award

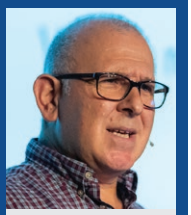
Gabriele Lignani (UCL) is the 2021 recipient of the Harinarayan Young Neuroscientist Award. Dr Lignani has led innovative research on a novel form of gene therapy for intractable epilepsy. The award is made every two years by the International League Against Epilepsy.

Kandel Prize


Julijana Gjorgjieva

Julijana Gjorgjieva (Frankfurt) is the 2021 winner of the Eric Kandel Young Neuroscientists Prize, awarded every two years by the Hertie Foundation and FENS. Dr Gjorgjieva studied for her PhD in Cambridge.

Vision grant


Leon Lagnado

Leon Lagnado (Sussex) has been awarded a £3m Wellcome Investigator Award to support research into the modulation of visual processing after exposure to a new visual environment or changes to the animal's body clock, using zebrafish as a model system. The award comes after two other Sussex researchers, **Tom Baden** and **Sylvia Schroeder**, received five-year grants from Wellcome to investigate the neural circuitry of vision.

Mental health

Marianne van den Bree (Cardiff) and colleagues have been awarded £3.6m by the MRC and NIHR to study the link between physical and mental health problems. The grant will enable research teams across the UK and Denmark to work together over the next four years as part of the Lifespan Multimorbidity Research Collaborative (LINC).

Blue plaque

A blue plaque has been created to honour neurologist **James Samuel Risien Russell**, one of the UK's first black or mixed-race consultants. Born in British Guiana (now Guyana), Dr Risien Russell was regarded as one of the UK's most important medical figures in the early 1900s and was appointed Professor of Medicine at UCL. The plaque will be displayed at 44 Wimpole Street, London.

AD award

Paul Fish (UCL) is the first UK-based researcher to receive an ADDF-Harrington Scholar Award from the Alzheimer's Drug Discovery Foundation (ADDF) and Harrington Discovery Institute at University Hospitals in Cleveland, USA. The award, worth up to US$600,000, will support work on an inhibitor of NOTUM, an enzyme that helps to maintain the integrity of the blood–brain barrier and is dysfunctional in some Alzheimer's disease patients.

Elaine Snell

The BNA was deeply saddened to hear of the death of Elaine Snell, our former Chief Operating Officer, in September 2021.

Elaine at a BNA Festival, flanked by Sir Colin Blakemore and Irene Tracey.

Elaine was BNA COO between 2012 and 2015 at a pivotal stage in the BNA's evolution. Elaine began the process of updating the BNA's organisation to ensure it could more fully be the voice of UK neuroscience.

Elaine played a key role in developing the BNA's first Festival of Neuroscience, held at the Barbican in London in 2013, which included an innovative public engagement programme. The event garnered extensive media coverage and set the template for future Festivals.

Elaine was a familiar figure on the neuroscience 'circuit', working for, among others, the International Neuroethics Society and the Lundbeck Foundation, organisers of the Brain Prize. She also worked with the European Dana Alliance for the Brain, supporting media activities at multiple FENS Forums, as well as with the Society for Neuroscience and the International Brain Research Organisation.

Elaine ran a series of lively and popular BNA-branded public engagement events at the Dana Centre in London. She was also a regular attendee at BNA Festivals and Festive symposia, renewing old friendships and forging new ones.

Before joining the BNA, Elaine had established a successful career in science communication, as head of media for the British Heart Foundation and the Wellcome Trust, and ran her own consultancy.

Russell Foster was President of the BNA when Elaine was COO: "I had the immense pleasure of working with Elaine whilst I was President of the BNA and as Chair of the Cheltenham Science Festival. During this time, I got to know Elaine well and she became and remained a close friend. She was a person of deep integrity, loyalty, generosity of spirit and, as all who knew her will remember, Elaine had the most wonderful sense of humour.

"Elaine had a deep and abiding commitment to the BNA. Elaine worked tirelessly to attract external benefactors to expand the financial base of the BNA; she supported and promoted at every opportunity early-career neuroscientists; and embedded the public understanding of science within all BNA activities. Elaine's tragic and sudden death has left her very many friends bereft, and the neuroscience community has lost a champion, advocate and innovator."

According to Anne Cooke, the BNA's current CEO: "Elaine's combination of openness, warmth and genuine enjoyment of people, along with being a superb communicator, advocate and organiser (she played a large part in organising her own commemoration, right down to the type of cake), meant her life was full of friends. It also meant that neuroscience benefited from someone who, from behind the scenes, enabled individuals to flourish and communities to grow. She will be greatly missed."

Elaine passed away peacefully on the evening of 20 September 2021 after a short illness. After the news was published on the BNA website, we received a host of messages saying how kind, welcoming and helpful Elaine was, and expressing sadness and shock at her untimely death.

Elaine had a warmth of character, enthusiasm and sense of fun that made her great company and an ideal workmate and friend. She will be greatly missed by all those who got to know her professionally and personally.

Some of the virtual tributes to Elaine

"Elaine was fantastic to work with and also great fun. This is such sad news. I shall miss her and miss the great gossips we had whenever we met up."
Emma Mason

"So so sad to hear this!! She was a wonderfully helpful and warm woman. Enjoyed her company both for work and leisure!!"
Trevor Bushell (Strathclyde)

"Very sorry to hear this news. Elaine was lovely to talk to. A great ambassador for neuroscience."
Hugo Spiers (Sussex) @hugospiers

"IBRO is sad to learn that Elaine Snell has passed away. She helped establish our Neuroethics Task Force responsible for implementing ethics curriculum components into IBRO schools. She was a champion of the global neuroscience community and will be deeply missed."
@ibroSecretariat·

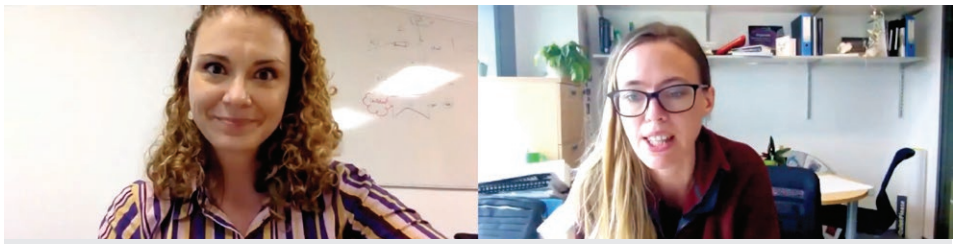
"Everyone at FENS is deeply saddened to hear of Elaine's passing. She has been a close collaborator and friend of FENS since its start in 1998. She will be greatly missed."
@FENSorg

"I'm speechless. Elaine was one of the kindest, most passionate and dedicated people I've ever met. Her contribution to global neuroscience and public engagement is enormous. I feel privileged to have known her and to have worked with her **@neuroethicsinfo @dana_fdn @SfNtweets**"
Marcello Ienca @Marcellolenca

"I am so sorry and sad to hear this. Elaine Snell was a wonderful person, who dedicated her career to public engagement with science. I feel privileged to have known her."
Sarah-Jayne Blakemore (Cambridge)
@sjblakemore·

Reproducibility in action

Three recent BNA webinars addressed the reproducibility of research involving induced neuronal cell cultures and brain organoids.



Iva Kelava (left) and Madeline Lancaster.

The BNA's 'Credibility in Neuroscience' initiative aims to promote reliable and reproducible neuroscience research. As part of this project, with funding from the Gatsby Foundation, the BNA organised a series of webinars on the reproducibility of research on induced pluripotent stem cells (iPSCs) and brain organoids – two increasingly popular neuroscience research tools.

Chaired by **Madeline Lancaster** (Cambridge), the three webinars focused on stem cell-derived cultures, organoids and use of such resources in industry.

Selina Wray (UCL) noted that variability was always seen between iPSC cultures, and recommended sourcing cells from multiple donors to address this variability. Although consistency is desirable, she noted that variability could be biologically important, potentially providing insights into clinical variability.

Alongside patient-derived iPSCs, it is now possible to engineer specific mutations into cells using CRISPR/Cas9 technology. Although this provides an isogenic background, and provides an opportunity to assess mutations that do not occur naturally, the chance to explore genetic modifier effects is lost. The NIH has created a set of engineered mutations relevant to neurodegenerative disease as a community resource.

One critical practical tip was not to neglect quality control (QC) – "boring but important", according to Selina.

Next up, **Iva Kelava** (Cambridge) provided an expert's guide to the development of brain organoids, 3D cultures with a tissue structure mimicking parts of the brain.

A wide range of factors can affect even normal tissue culture and introduce variability, and this complexity is multiplied by 3D culture. Starting culture has a major impact on organoid formation, while the batch effect – different behaviour of cultures started on different days – is a further critical factor.

Iva recommended choosing a model based on a scientific question of interest rather than rushing to adopt a new technology. Other practical tips included having a good understanding of the target tissue type and brain region, always checking the molecular identity of structures analysed, and examining multiple parameters to assess organoid properties.

Some QC can be outsourced through use of commercially available kits, while an online community has been established to provide technical support. Iva also floated the idea of a biobank of well-characterised cell lines and organoids.

In the final webinar, **Clare Jones** (Talisman Therapeutics) provided an industry perspective. She summarised the approach taken to generate cell models and assays, emphasising the critical importance of QC at all stages, comprehensive recording, standardising protocols, and training of staff. She suggested that the rigour of research was typically higher in industry, as data supported financial investments that could make or break a company rather than primarily being the route to a high-profile academic paper.

Raising the need for credibility in research within Parliament

The BNA has responded to a Parliamentary inquiry on reproducibility in research, highlighting that a wide variety of stakeholders need to take action to help strengthen research, improve research careers, and boost credibility in research as a whole.

The House of Commons Science and Technology Committee is reviewing reproducibility across research, gathering a mix of written and oral evidence before issuing recommendations to government and the research sector. In the BNA's written response, we call for changes to strengthen reproducibility of research – including rewarding researchers' contributions to open and reproducible science, funding infrastructure to make research more transparent, challenging the standard publishing model, and placing pre-registration at the heart of research assessment.

We are also supporting partner organisations to respond to the inquiry – including the UK Reproducibility Network, of which the BNA is a founding member of the stakeholder group. The network has been boosted with news of £4.5m funding from the Research England Development Fund, which will help to expand its training on open research practices across the UK.

Our Credibility Advisory Board has been invaluable for helping inform the BNA's work, including its responses to this inquiry. This was one of the final pieces of work that **Dorothy Bishop** (Oxford) helped on before stepping away from the Board ahead of retirement. A celebrated scourge of 'bad science', Dorothy has been an ardent supporter of the open and reproducible science movement, and we thank her for helping to establish our work on credibility at the BNA.

The webinars are available to view online on the BNA's YouTube channel (see **https://bnacredibility.org.uk/recordings**).

Community-based credibility

Credibility is critical in preclinical research. Annesha Sil and Gernot Riedel describe some of the steps being taken at the University of Aberdeen to ensure credibility in preclinical neuroscience research.

Preclinical biomedical research, especially in disciplines such as neuroscience, has been under scrutiny for low levels of reproducibility across laboratories, culminating in what is commonly referred to as the 'reproducibility crisis'. The Translational Neuroscience laboratories headed by **Gernot Riedel** and **Bettina Platt** at the Institute of Medical Sciences (IMS) at Aberdeen University have recognised an urgent need to address this crisis and have played an integral role in several initiatives relevant to increased credibility in neuroscience.

The Riedel/Platt research groups specialise in studying mechanisms of neurodegenerative disorders. These are investigated through a wide range of techniques including behavioural and metabolic testing, EEG, tissue analysis using Western blotting, quantitative PCR, microscopy and histology, cell culture assays, and imaging.

In our efforts to tackle the reproducibility crisis, we have been key members of the **EQIPD (Enhancing Quality in Preclinical Data) consortium**, funded in 2017 by the EU's Innovative Medicine Initiative (IMI2) under the umbrella of Horizon 2020. This consortium has brought together more than 30 academic institutions and pharmaceutical companies from eight countries to improve robustness and reproducibility of preclinical research (**https://quality-preclinical-data.eu**).

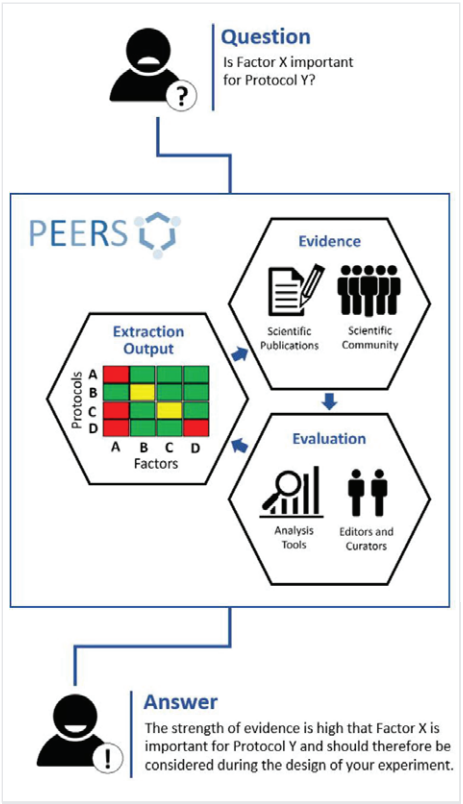
As a consortium member, we have helped to design a comprehensive framework to ensure rigour in the design, conduct and analysis of animal experiments, and have experimentally applied these guidelines to improve reproducibility in an international multi-laboratory study involving animal sleep–wake EEG. Furthermore, we were integral in developing and beta-testing a novel preclinical research quality system (EQIPD-QS) that seeks more data transparency and traceability from design to performance and analysis of experiments [1]. We have trialled the quality system in Aberdeen and became the first UK research laboratory to be accredited for being EQIPD-QS compliant.

A second approach is the development of an online open-access platform to help scientists determine which experimental factors and variables are likely to affect the outcome of a specific test, model or assay and therefore ought to be considered during the design, execution and reporting of experiments. This pan-European project, **PEERS (Platform for Exchange of Experimental Research Standards)**, is currently funded by a US organisation, Cohen Veterans Bioscience, and hosted on its servers (**https://www.braincommons.org/peers-platform/**).

The PEERS database is categorised into *in vivo* and *in vitro* experiments and provides lists of factors derived from the scientific literature that have been deemed critical for experimentation. The '3Es' of the system include each publication (Evidence), which is rated by multiple experts for the quality of its methods and results (Evaluation) on scorecards. Multiple scorecards provide the Extracted output freely accessible to every registered user.

PEERS provides a way to search for information to ensure experimental rigor prior to embarking on an experiment. It also encourages engagement of the scientific community using a wiki-like approach to expand the information contained within the platform by rating of the evidence or by introducing new protocols through a standardized approach to data curation. To introduce PEERS to the scientific community, we have recently submitted our first publication and published a preprint describing the features of the database [2].

Ultimately, efforts to improve reproducibility and robustness of experimental data require a massive collaborative effort and active participation of the wider scientific community. Therefore, we invite researchers at every level, especially those early in their careers, to contribute to PEERS so that it can become a comprehensive and widely used tool in the neuroscience community. Through our combined efforts, we believe that initiatives such as PEERS will serve as an effective collaborative exchange and analysis tool to enhance data validity and robustness and the reproducibility of neuroscience research.



A graphical summary of PEERS, from Ref. 2.

• **Annesha Sil** (annesha.sil@abdn.ac.uk) and **Gernot Riedel** (g.riedel@abdn.ac.uk) are in the Institute for Medical Sciences, University of Aberdeen.

1. **Bespalov A *et al***. Introduction to the EQIPD quality system. *Elife*. 2021;10:e63294.
2. **Sil A *et al***. PEERS - an open science "Platform for the Exchange of Experimental Research Standards" in biomedicine. *bioRXiv* 2021. doi: https://doi.org/10.1101/2021.07.31.454443

Mapping the rat brain

***Brain and Neuroscience Advances* is proud to have published – and made freely available globally – a detailed new atlas of the rat brain.**

The rat is one of the most popular model organisms in behavioural neuroscience research. In the UK, one particular strain, the Lister hooded rat, is typically the animal of choice for such studies.

Research into the specialised functions of different regions of the brain, and their connectivity, are dependent on brain atlases that can be used to locate the regions to be targeted for electrode insertion for recording of neural activity or ablation of specific neural tissue. These brain atlases provide three-dimensional coordinates to guide stereotaxic surgery.

Brain atlases have typically been carefully constructed from detailed histological data. This raises the possibility that distortions may be introduced during preparation of histological samples. In addition, brain atlases have not been specifically developed for the Lister hooded rat and there is likely to be some minor variation in brain structure between rat strains.

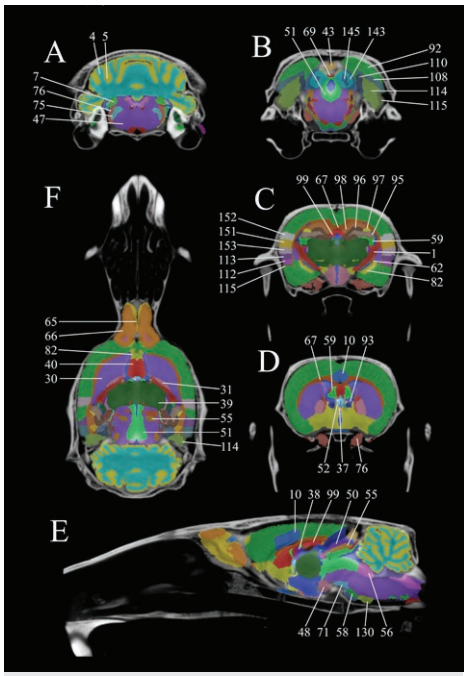
Coordinates derived from traditional atlases therefore give only approximate coordinates for the location of brain regions in the Lister hooded rat, and accurate coordinates typically have to be identified though pilot surgery.

To address these issues, researchers from Nottingham and Magdeburg, Germany, have used MRI to generate a new brain atlas – known as 'Ratlas' – specifically for Lister hooded rats [1].

The new atlas is based on MRI of seven animals, with images combined to create an average rat brain. This was then combined with averaged CT images of the surrounding skull, which provide structural 'landmarks' to guide stereotaxic surgery.

Labels were added to aid identification of different brain regions, while the digital nature of Ratlas will make it accessible and easy to use. As *Brain and Neuroscience Advances* is a 'gold' open access journal, the resource will be freely available to researchers all over the globe.

Ratlas will be an essential resource for all researchers using Lister hooded rats in their research. Furthermore, by providing a more accurate set of coordinates for brain regions, it will reduce the need for pilot surgery and ensure more refined use of animals, contributing to the '3Rs'.



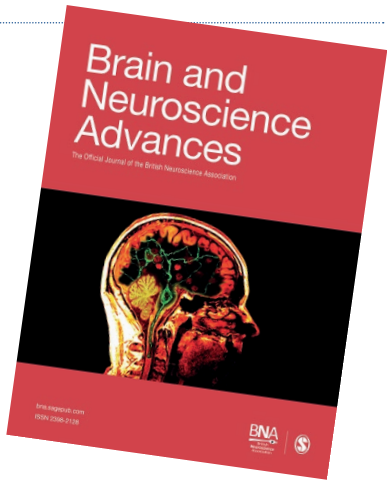
Selected views from Ratlas-LH; see Ref. 1.

New content

Among the other papers recently published in *Brain and Neuroscience Advances*, **Emma Robinson** (Bristol) and colleagues have explored apathy in aged mice [2]. Apathy is seen in a range of neurodegenerative conditions and during ageing, and can have a profound impact on quality of life. While generally seen as a motivational disorder, apathy seems to affect a range of neurocognitive domains.

Using a battery of tests, Robinson and colleagues identified a range of apathy-related deficits in aged but otherwise healthy mice, across domains such as motivated behaviour, reward sensitivity and emotional reactivity. The work suggests that aged mice could be a valuable model for studying the psychiatric symptom of apathy and ways to treat it.

In April 2021, BNA*2021*: Festival of Neuroscience was held online. *Brain and Neuroscience Advances* has now published the full set of poster abstracts from this highly successful meeting [3].



Negative urgency

A dozen articles have been submitted to *Brain and Neuroscience Advances'* new special collection focusing on 'negative urgency' as a driver for psychopathology. The special collection is being edited by **Donald R Lynam** (Purdue University) and **Jeffrey W Dalley** (Cambridge). Negative urgency is the tendency to act rashly when experiencing extreme negative emotions, and its importance is increasingly being recognised in a range of neuropsychiatric disorders. The deadline for this special collection has been extended to the end of October 2021.

All *Brain and Neuroscience Advances* 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**.

1. **Prior MJW, Bast T, McGarrity S, Goldschmidt J, Vincenz D, Seaton A, Hall G, Pitiot A**. Ratlas-LH: An MRI template of the Lister hooded rat brain with stereotaxic coordinates for neurosurgical implantations. *Brain Neurosci Adv*. 2021 Aug 10;5:23982128211036332. https://doi.org/10.1177/23982128211036332.
2. **Jackson MG, Lightman SL, Gilmour G, Marston H, Robinson ESJ**. Evidence for deficits in behavioural and physiological responses in aged mice relevant to the psychiatric symptom of apathy. *Brain Neurosci Adv*. 2021 May 25;5:23982128211015110. https://doi.org/10.1177/23982128211015110.
3. BNA 2021 Festival of Neuroscience Poster abstracts https://doi.org/10.1177/23982128211035062.

Getting to know your BNA

A lynchpin of the BNA, in September 2021 Louise Tratt reached a major milestone – ten years at the BNA. Who better to feature in this issue's 'Getting to know your BNA'.

Name: **Louise Tratt**
Job title: **Executive Officer**
Joined the BNA: **2011**

Role in a nutshell

Wow, this is a tough question as the role of Executive Officer has evolved so much over the 10 years that I have been in the post! In a nutshell, it is the first point of contact for the BNA. My job share (Hannah Thurgur) and I pick up the office emails and deal with the daily office tasks, but alongside this there are many other projects and tasks which we each dive into and take responsibility for, which is what I really enjoy about the role – nothing is off the cards. Anne Cooke sometimes describes us as the 'beating heart of the BNA'!

Best thing about working at the BNA

Without sounding cheesy, the best part is the real sense of belonging to a family. There is a real community spirit and within the BNA Executive team we have a blast. At real-life meetings (which will hopefully return soon), there is nothing like catching up with neuro friends over a drink.

I especially love the sense of fun within the organisation. We don't just run a standard neuroscience conference, we put on a Festival of Neuroscience, a real show, complete with rappers, speed-dating, and ceilidh dancing! More recently we ran a fancy-dress competition, 'Robe your Lobes', alongside our annual Festive Symposium, which was online for the first time. I came as a flapper girl from the roaring 20s and there was a great sense of fun all round.

BNA goals for the next year

I think this would be just to do my job to the best of my ability. My youngest child has recently started school so I feel I can really focus now and put my best into my work. I very much enjoy the events side of the job and hope to be able to grow in confidence with delivering online events, especially as the events climate has drifted so drastically and we, as the BNA, are delivering many more virtual events.

Louise Tratt

Dream job

I always wanted to be a popstar when I was younger, but do not have a voice like Beyoncé! Otherwise, I do not really have a dream job as such – just a job that allows a good work–life balance with time for the beach.

Favourite place

The beach! I was born and bred in north-west London, but I have always been drawn to the coast, wherever it may be, and have been living in Lyme Regis now for over 13 years. I try to go to the beach most days – it is like therapy for me.

Book/film/music that had the biggest impact on you (and why)

Anne Frank's *The Diary of a Young Girl*. I remember reading it at school when I was 13/14 and being able to relate to Anne in some ways. I loved her witty sense of humour and the characters she gave to her housemates. I have recently re-read it and find it just as powerful. Having visited the Secret Annex in Amsterdam some years back added an extra dimension to the book the second time round.

Most surprising thing people may not know about you:

Ha, there is not much as I am a bit of an over-sharer! I am a fully qualified spray tan therapist, I once had a stint as a Butlins Redcoat, and I can juggle!

Dates for the diary

- **9 November 2021**: Building bridges along the psychiatric drug discovery pipeline – challenges and opportunities for collaborative partnerships (with the Psychiatry Consortium)
- **23 November 2021**: Building bridges along the psychiatric drug discovery pipeline – understanding and prioritising patient unmet need (with the Psychiatry Consortium)
- **10 December 2021**: FORUM Networking event: Understanding chronic pain (with the Academy of Medical Sciences)
- **13 December 2021**: BNA Festive symposium 2021
- **22 February 2022**: Building bridges along the psychiatric drug discovery pipeline – the academic perspective of the challenges of drug discovery (with the Psychiatry Consortium)
- **8 March 2022**: Building bridges along the psychiatric drug discovery pipeline – the industry perspective of the challenges of drug discovery (with the Psychiatry Consortium)
- **22 March 2022**: Building bridges along the psychiatric drug discovery pipeline – solutions of how to work together (with the Psychiatry Consortium)
- **27–28 April 2022**: BNA Members' Meeting
- **11 May 2022**: Building Bridges Between: Industry and Academia (Sainsbury Wellcome Centre, London)

See **https://www.bna.org.uk/mediacentre/events/** for full details.

New members

A very warm welcome to all those who have joined the BNA since the last issue of the BNA Bulletin was published:

- Adchaya S R
- Aiste Viduolyte
- Alexander Akinjayeju
- Alice Purvor
- Ally Hughes
- Amélie Lothe
- Andrei Varga
- Andrew Sutherland
- Andrew Toft
- Anna Hows
- Annabel Laver
- Anne Baron
- Anusree Sreedeep Nair
- Ayesha Pointer
- Baraa Wahishi
- Bethany Hirons
- Beverley Isherwood
- Bishr Shibani
- Brook Perry
- Busra Perihan Yucel
- Carmen Maria Leiner
- Clive Sherwood
- Csilla Talamasz
- Daniel Berg
- Daniel Callaghan
- Daniela Fernandois
- Deryn Bishop
- Douglas Lopes
- Ece Karabulut
- Elisa Nent
- Emily Herrod
- Esra Hassan
- Eugenia Kuteeva
- Ezra Ahn
- Fadil Karim
- Faisal Rehman
- Faith Howard
- Fei-Yang Huang
- Francesco Scaramozzino
- Gabbie Portlock
- Gabriele Richardson
- Gavriela Alexandrou
- George Goodwin
- Georgia Walsh
- Gerard Loquet
- Grace Woolway
- Halimatu Hassan
- Hazem Toutounji
- Hinze Ho
- Isabella Colic
- Jack Wood
- Jacopo Cocciarelli
- James Moran
- Jasminka Mitrovic
- Javaria Syed
- Jayant Saha
- Jennifer Cook
- Joe Freeman-May
- Joshua Jacob
- Karolina Farrell
- Karolina Talandyte
- Kay Hamilton
- Keith Robertson
- Kelly Vanstone
- Kenneth Wood
- Kirstie Cronin
- Laura Ajram
- Laura Shippey
- Lena Franzen
- Lianne Weaver
- Lilian Alcaraz
- Livia Jacqueline Florentine Versprille
- Lucas Ortega
- Maisha Maliha Promi
- ManSze Yeung
- Manu Kumar
- Maria Roznovcova
- Maria Shoshorina
- Marina Thwaites
- Matthew Albrighton
- Megan Roberts
- Mia Raso
- Michael Bale
- Milena Rota
- Millie Wilson
- Moataz Badawi
- Moyra Akure
- Natruedee Potiwat
- Nerys Feeney-Howells
- Niamh Conway
- Nicole Coutinho Garrido
- Nicole Vissers
- Paresha Thind
- Patricia Garcia
- Patrisia Hincheva
- Petrova C Fairhurst
- Phillipa Timmins
- Priscilla Yowa
- Priya Viswanathan
- Rachel James
- Randeep Rai
- Robert Turley
- Rodrigo Bammann
- Rory Gosling
- Rute Marques
- Saakshi Sharma
- Samantha Morris
- Samuel Shields
- Samuel Winiarski
- Sana Ali Syeda
- Shalini Mani
- Sian Constantine
- Simon Bennett
- Sonia Gandhi
- Sophia Eugenia Hodgkinson
- Sophie Haig
- Sophie Hawkins
- Sophie Nyberg
- Sophie Rustidge
- Sophie Schofield
- Sophie Smart
- Stella Goeschl
- Stephanie Churcher
- Sylvia Sidorowicz
- Talia Gileadi
- Tamara Boto
- Tara Middlehurst
- Thanh-Tuyen Tran Nguyen
- Torbjörn Waerner
- Vasanta Subramanian
- Victoria Cowling
- Vithya Helbig
- Wajid Farid
- Yash Kacha
- Yihe Lu

MEMBERSHIP OPTIONS

There are many great reasons to join the BNA, and many membership options too:

- **Undergraduate/student**
- **Postgraduate**
- **Career Starter**
- **Early Career**
- **Full/Industry**
- **Associate**
- **Retired**

We also offer a bulk membership scheme, research group member scheme, gift subscriptions, and the possibility of reduced fees through our equity and diversity initiative.

Don't forget that the benefits of BNA membership include free membership of FENS, access to reduced fees for the US-based Society for Neuroscience (SfN) annual meeting, eligibility for prizes, bursaries and funding – and much more.

Check out full details at **https://www.bna.org.uk/about/membership/**

The following article has been supplied by one of our sponsors, whose support is gratefully acknowledged.

Building bridges along the psychiatric drug discovery pipeline

At the Psychiatry Consortium, we believe the challenges facing psychiatric research require the insights and involvement of individuals across all aspects of the research landscape. People with lived experience of mental health, academic researchers, clinicians, regulators and industry scientists, to name a few, must all be involved in the development of solutions if we are to overcome the hurdles to psychiatric drug development.

We're proud to launch a series of webinars in partnership with the BNA, to highlight the challenges and opportunities at key stages in the translational pipeline. The series will span the whole process, from identifying unmet patient need, undertaking basic research required to understand the disease biology to developing novel treatments. At each stage, we will hear from experts who will give their perspectives on what we can do to support each other along this process.

"DRUG DISCOVERY IS ABOUT RELATIONSHIPS AND HUMAN INTERACTION – THE MORE HUMAN YOU CAN MAKE IT, THE BETTER" – MATT EAGLES, HEAD OF PATIENT ENGAGEMENT, HAVAS LYNX GROUP

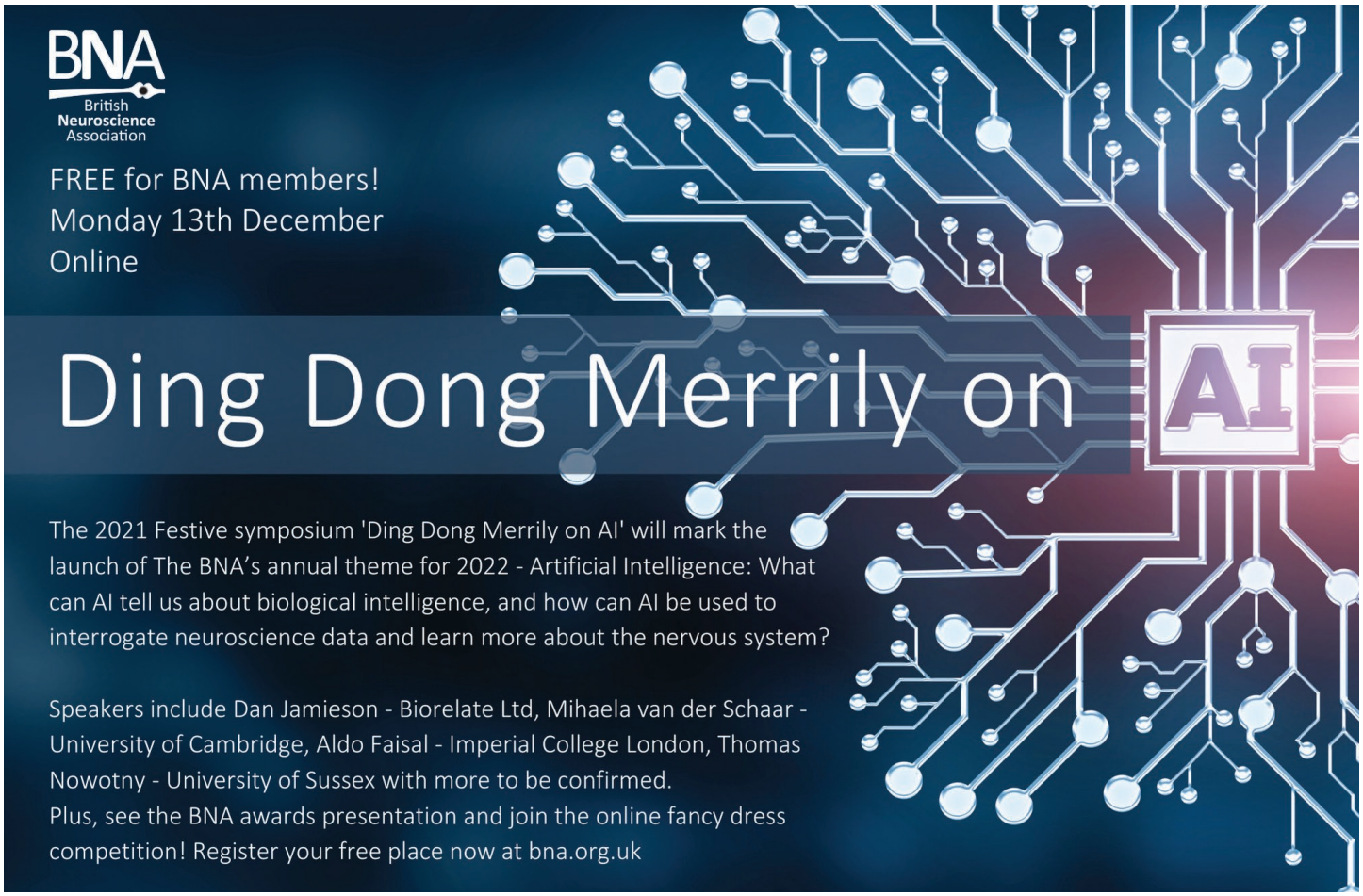
We hope this series will humanise the research 'story' and provide opportunity to openly discuss the different stages of the research pipeline from all perspectives, so that we can all understand, or at least be aware of, the challenges that different sectors are trying to overcome, and work together more fruitfully in future.

We welcome you to join us at the upcoming webinars:

- **Tuesday 9 November 2021 1–2pm** (GMT) Overview of the key challenges facing psychiatric drug discovery and how the BNA and Psychiatry Consortium are working together to address them
- **Tuesday 23 November 2021 1-2pm** (GMT) How can we better understand unmet patient need, and feed this into drug discovery efforts?
- **Tuesday 22 February 2022 1–2pm** (GMT) The academic perspective of the challenges of drug discovery and solutions to overcome them
- **Tuesday 8 March 2022 3–4pm** (GMT) The industry perspective of the challenges of drug discovery and opportunities for collaborations with academia
- **Tuesday 22 March 2022, 1–2pm** (GMT) Building bridges – how to work together and how best to 'hand over the baton' to the next in the line

To register, go to **www.bna.org.uk/mediacentre/events/** or **psychiatryconsortium.org/events/**

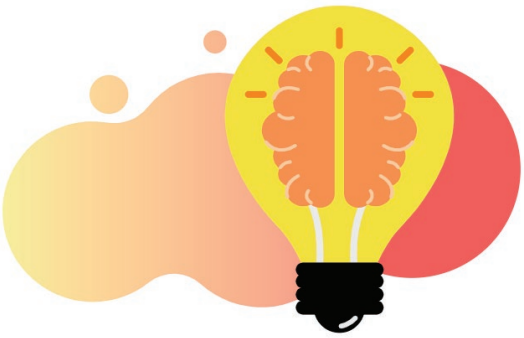
This webinar series is supported by the Gatsby Foundation.



Issue No. 5
Autumn 2021

BRAIN INSIGHTS

NEWSLETTER



Society has witnessed considerable change to both science and policy in recent years on both a national and international scale. In terms of methodological changes to scientific practice, there is an ever-increasing implementation of replicable open science research, to which the BNA is firmly committed, and which has been a topic of interest in our prior articles.

Considerable progress in medical research has also been made, including advances in the utility of portable MRI systems for assessing patients at risk of critical injury or for whom conventional imaging may be impractical (e.g. paediatric populations) and a myriad of discoveries pertaining to infectious diseases. Over the last 18–24 months, monumental leaps in the scientific understanding of infectious diseases have taken place, most notably research and clinical investigation into COVID-19, some of which are covered in this issue.

Specifically, this edition of Brain Insights opens by delving into historical perspectives in neurology, exploring visual processing in Capgras syndrome. Next, in the context of perception and problem-solving, we consider the origins of 'insights', before opening up another prevalent perspective on health and disease via the gut–brain axis. Broadening our cerebral sphere, our writers discuss neurodegenerative disease research through the lens of not only neuronal interactions, but also those of astrocytes in the context of Alzheimer's disease, alongside potential associations between dementia and infectious diseases such as COVID-19, wherein cognitive capacity may play an important role in adherence to guidelines in order to minimise the likelihood of infection. A therapeutic perspective thereafter highlights the utility of antisense oligonucleotide therapies, small interfering RNAs, and gene editing in Huntington's disease, before we close by examining links between epilepsy and COVID-19, and the processing of alcohol on its journey from gut to brain.

My fellow editors and I hope you enjoy this issue, which is wholly possible due to the wonderful contributions or our writers. If you are interested in writing an article for Brain Insights, or collaborating in any form, feel free to get in touch using our details below.

Ryan A Stanyard

In this issue:

- **Ben Stocker**: Historical Perspectives in Neuroscience: What is Capgras syndrome?
- **Bilyana Batsalova**: The patient genius
- **Daniel Dabbs**: The relationship between the gut and brain
- **Samah Sabreen**: Astrocyte-mediated synapse elimination in Alzheimer's
- **Georgia Walsh**: Understanding the relationship between dementia and COVID-19 risk
- **Maria Zareef Kahloon**: Is antisense oligonucleotide gene therapy the way forward for treating Huntington's disease?
- **Laiba Ejaz**: Epilepsy and COVID-19: A potential link?
- **Baraa Wahishi**: Alcohol and the brain

• Versions of articles with references can be found on the BNA website.

If you have ideas or suggestions for *Brain Insights*, or would like to get in touch, please contact us:

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Historical Perspectives in Neuroscience: What is Capgras syndrome?

Ben Stocker, Second-year Psychology Student at the University of Portsmouth

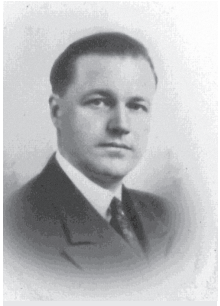
"YOU LOOK LIKE MY MOTHER... BUT YOU ARE AN IMPOSTER!"

Capgras syndrome (CS) is a rare neurological condition. It was first described in 1923, by psychiatrist Joseph Capgras in a case of a 53-year-old woman, who held the delusional belief that those she knew had been replaced by imposters.

Capgras adopted a Freudian view of repressed human sexuality, suggesting damage to the brain resulted in fragmentation of the ego, allowing sexual urges to 'rise to the surface'. The rapid surge of sexual urges would not have been experienced since childhood, suggesting that CS resulted from an interpersonal conflict when the patient was confronted with such emotions. However, this theory was insufficient to adequately explain the condition, as in the case of a patient who believed that his pet poodle, Fifi, was an imposter.

Ramachandran and colleagues later proposed a neurologically based explanation for CS, integrating prominent visuo-perceptual regions of the brain, including the fusiform face area (FFA) and the amygdala. This model proposed that CS arose when trauma occurs between the FFA, amygdala and other parts of the limbic system.

To understand this syndrome, the neural processes of face visualisation must first be explained. The main components are the optic nerve and associated tract, lateral geniculate body, primary visual cortex and the FFA. The function of the FFA is to discriminate faces from other objects. When the FFA–visual pathways are intact, a patient can discern faces. The FFA relays visual information along a subcortical, collicular–pulvinar path to the amygdala, where emotional valence is associated with the face. The colliculus and pulvinar nucleus of this path are both involved in visual attention processing, so damage to this path may render an individual unable to attach emotion to a significant other – hence the expression: "you look like my mother... but you are an imposter".



Joseph Capgras.

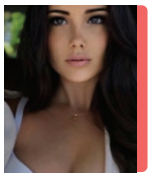
Ramachandran's model is predicated on two separate neurological pathways existing when facial stimuli are perceived and emotion is attached to them, as proposed by Ellis and Young. The ventral (underside) stream – the primary visual pathway – is considered intact, allowing the patient to identify the individual before them correctly, while damage to the dorsal (upper side) pathway – mediating visually guided goal-oriented action – can result in an inability to attach emotional meaning to a face (although recent evidence suggests greater modulation occurs via the ventral stream). The amygdala is essential for the mental evaluation of emotional facial expressions. Where individuals suffer unilateral or bilateral amygdala lesions, they are unable to perceive emotionally driven facial cues. Incorporating social and emotional cues is necessary to identify a familiar face – a function apparently lost in CS. According to the models of Ellis and Young, the amygdala forms a vital component of the dorsal pathway. With damage to the amygdala, pre-amygdala or any path post-FFA, neuronal activity cannot be passed through the amygdala. Hence, the patient feels a lack of emotion towards their significant other.

Typically, post-amygdala, messages are cascaded to the autonomic nervous system, causing elevated heart rates and changes in the galvanic skin response (GSR). Upon seeing a stimulus, the individual finds it emotionally important, significant or exciting; they sweat in response, stimulated by their sympathetic nervous system. This is quantifiable through electrode analysis of their GSR. However, Ramachandran found abnormally flat GSR responses in CS patients presented with images of their parents, indicative of potential sub-threshold amygdaloid responses to faces in CS. A heightened state of arousal would typically be expected as amygdala activity has been associated with both positive feelings (e.g. warmth) and negative feelings (e.g. pain associated with another individual).

CS is specific to visual defects; patients can recognise people from other sensory cues, such as smell or sound. For example, Ramachandran describes a case where a patient used a telephone to communicate with his mother in an adjoining room. He could perceive his mother's voice but could not recognise her face. A separate pathway exists between the auditory cortices and the olfactory cortices to the amygdala. In addition, a pathway exists for auditory processing, travelling via the cochlea to the medial geniculate nucleus, located in the thalamus, then to primary auditory cortex and the amygdala. This network activation underlies an emotional response.

The number of CS cases may exist alongside a diversity of other conditions, including pseudohypoparathyroidism, diabetes and subarachnoid haemorrhages. Cases without previous medical history have been observed, suggesting an organic origin. Several experimental studies have associated CS symptoms more with the right hemisphere than the left, reinforced by case studies using EEG, GSR, fMRI and cerebrospinal fluid analysis. This evidence suggests that right hemispheric dysfunction is central to the development and expression of CS.

The comparisons between Capgras's 1923 psychodynamic-based model and modern neuropsychiatric interpretations are fascinating, as neurotechnology and knowledge have since greatly increased. Many additional cases from around the globe have now been identified, and present with a vast array of pre-existing conditions, psychiatric influences and diverse family history.



The patient genius

Bilyana Batsalova, Second-Year BSc Neuroscience Student at KCL

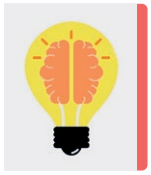
Coming up with a new idea or a novel discovery can seem difficult – a superpower only available to the once-in-a-generation genius. Insight arises when an individual interprets a stimulus, situation, or event to produce a non-obvious, non-dominant interpretation. Prior to an insight, an increase in alpha-band oscillations (10–12 Hz) associated with neural inhibition occurs in sensory areas such as the visual cortex, suggesting that processing of external information is inhibited. In addition, alpha oscillations may reflect sensorimotor inhibition, while eye-tracking experiments suggest that insightful problem-solving is associated with an interruption of visual input.

There is some evidence that Eureka moments can be created by frequency-specific non-invasive brain stimulation, in which high-frequency synchronisation plays an important role in the coordination of activity relevant for cognition. Further, gamma activity (40 Hz) may be involved in the multistep process behind the emergence of insight, considering its involvement in a wide range of cognitive processes (e.g. neural binding). In the right temporal pole, gamma activity increases before participants solve a problem, as observed in chess players.

EEG and fMRI studies have identified enhanced connectivity of the bilateral temporal lobes (fMRI) and activation of the right anterior temporal lobe (EEG) following electrical stimulation of alpha and gamma activity in the right parietal and temporal lobes using transcranial alternating current stimulation (tACS) while participants completed verbal or visuospatial puzzles. Specifically, 40 Hz tACS stimulation elicited increases in gamma EEG spectral power, related to lexical and semantic processing on which Eureka moments are thought to be contingent. Similarly, 40 Hz stimulation increased accuracy on a verbal task by 20%.

Resting-state fMRI connectivity analyses suggested a positive correlation between bilateral temporal connectivity and the cognitive enhancement induced by 40 Hz tACS stimulation. Overall, this study suggests that an increase in fast oscillatory neuronal activity may serve as a potential substrate for organising sensory information so as to bolster problem-solving.

In summary, the chances of a Eureka moment depend on our ability to draw on a wealth and breadth of knowledge, which increases our capacity for associations between different areas. Human perspective is nourished by a wider associative context, enabling conversion of information consolidated in the unconscious over time into a conscious stream or 'insight'.



The relationship between the gut and brain

Daniel Dabbs, MRes Stem Cell Neurobiology Graduate, Cardiff University

"ALL DISEASE BEGINS IN THE GUT" *Hippocrates*

To what extent does the pathology in our gut impact our brain? In the 1800s, Willian Beaumont treated a patient with a fistula (abnormal passage between two epithelial surfaces) in his gut, and noted that whenever the subject "became angry or irritable, it greatly affected the rate of digestion", providing one of the earliest links between the brain and gut.

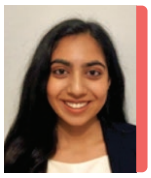
The bidirectional pathway of brain–gut signalling includes the central nervous system (CNS), autonomic nervous system (ANS), enteric (gastrointestinal) nervous system, and the hypothalamic–pituitary–adrenal (HPA) axis. The ANS allows afferent signals from the intestinal lumen to be transmitted through the enteric, spinal and vagal nerves to the CNS, with efferent signals from the CNS being sent to the intestine. The HPA axis regulates release of cortisol, a multifunctional hormone targeting multiple organs, which is involved in mechanisms of stress and immune responses. Thus, neural and hormonal pathways combine to allow the brain to interact with neuroimmune and neuroendocrine aspects of the intestine.

Recent evidence suggests that the gut microbiota, microorganisms that reside in the gastrointestinal tract, influence communication with the brain. Germ-free rodents display reduced anxiety-like behaviour and neurochemical changes, rodents given specific strains of bacteria show anxiety-like behaviour in the absence of an immune reaction, and faecal microbiota transplantation from subjects with neurological disease can induce phenotypes in animal models. The brain can interact with the gut microbiota through bacterially produced neurotransmitters or a range of microbe-derived metabolites.

Other researchers investigated depression in people with irritable bowel syndrome given *Bifidobacterium longum*, a probiotic (microorganism beneficial to health). Depression scores in the probiotic-treated group were significantly reduced and functional changes in the amygdala and fronto-limbic regions were observed using fMRI, highlighting activation of brain regions involved in memory, behavioural regulation and emotional responses.

In Parkinson's disease (PD), gastrointestinal dysfunction is often seen before the development of motor symptoms. Further, a meta-analysis of bacterial sequence data has revealed dysbiosis associated with PD.

Collectively, this body of evidence suggests a novel link between the gut and brain with implications for multiple diseases.



Astrocyte-mediated synapse elimination in Alzheimer's

Samah Sabreen, Third-Year Neuroscience MSci Student at KCL

Alzheimer's disease (AD), a progressive brain disease, is a leading cause of disability and dependency among older people, with an estimated 28.8 million human years lost to disability. Research has primarily focused on the protein hallmarks of AD, such as amyloid beta and tau, but recently the role of glia in synaptic loss has begun to gain increasing attention. In particular, astrocytes, once thought to be key homeostatic regulators of the brain, are implicated in synaptic loss – a primary correlate of AD. Astrocytes are now understood to play a critical role in synaptic pruning, refinement of neural networks that is essential for development of the healthy adaptive brain and a promising new avenue for AD research.

Emerging evidence suggests that astrocytes have a far more involved and invasive role in regulating synaptic health, particularly through phagocytic mechanisms. Phagocytosis is a highly regulated process in which threats such as pathogens and debris, including aged synapses, are eliminated to maintain neural circuitry development. It is mainly thought to be performed by microglia, the resident macrophages of the brain, but is now known to be also carried out by astrocytes – particularly when compensating for microglial dysfunction. Upon ageing and predisposition to genetic risks, phagocytosis is dysregulated. This causes a build up of senescent synapses that cannot be cleared effectively by astrocytes, implicating the downstream immune response system – the complement system.

The complement system is hyperactive in both AD risk groups and AD patients. This system plays an important role in the maintenance of homeostasis and in the sculpting of brain architecture. Among other factors, this system is overstimulated due to the accumulation of non-functional synapses, which are subsequently tagged by the C1q protein – the initiator protein of the classical complement cascade. C1q aggregates, which mark these synapses for opsonisation, commence a proteolytic cascade involving a multitude of complement proteins, all which are shown to become upregulated in AD patients. This subsequently induces mast cells, a type of white blood cell, to release proinflammatory molecules and recruit other immune cells. Thus, this redirection and overcompensation due to defective astrocytic synaptic pruning creates a highly inflammatory microenvironment, ultimately facilitating the loss of functional excitatory synapses – imperative for memory circuitry.

In summary, astrocytes may play a significant role in AD pathology. Investigating this interaction further, along with other glial-inclusive approaches, may yield new insights that could translate into novel therapeutic targets and strategies for AD.

Understanding the relationship between dementia and COVID-19 risk

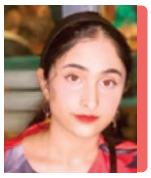
Georgia Walsh, Third-Year Biological Sciences student at Durham University

COVID-19 rapidly evolved into a worldwide pandemic after first emerging in December 2019. Underlying health conditions, such as chronic lung diseases, increase the risk of severe COVID-19 infection, with increased prevalence with age. Similarly, dementia, including Alzheimer's disease (AD), has an increased prevalence with age and, as patients often live with one or two additional health conditions, which overlap with known COVID-19 risk factors, there are suggestions that these individuals are more susceptible to COVID-19 infection and mortality.

In a recent UK Biobank study, a pre-existing diagnosis of dementia was found to be associated with not only the largest risk of testing positive for COVID-19, but also COVID-19-related mortality, when data from 13,338 volunteers were analysed. Similar findings were demonstrated in a larger study of 20,133 patients across England, Scotland and Wales who were enrolled in the International Severe Acute Respiratory and emerging Infections (ISARIC) World Health Organisation (WHO) Clinical Characterisation Protocol UK (CCP-UK) study, which found that dementia and other chronic neurological disorders correlated with increased hospital COVID-19 mortality. This association between dementia and an increased risk of both COVID-19 infection and mortality was also reported in the USA following analysis of patient electronic health records for approximately 61.9 million adult and senior patients, with the strongest effect identified for vascular dementia after adjusting for differences in age, sex, race and other risk factors.

The question therefore arises as to why a pre-existing diagnosis of dementia increases COVID-19 risk. From a biological perspective, pathological examination of post-mortem tissue from AD patients revealed an upregulation of the angiotensin-converting enzyme 2 (ACE2) receptor, the receptor used by the SARS-CoV-2 virus to enter host cells. This, combined with increased permeability of the blood–brain barrier in those with dementia, may result in higher viral entry into cells, predisposing individuals to a more severe COVID-19 infection.

In addition, the behavioural and psychological symptoms of dementia, such as cognitive decline, may compromise the ability of individuals to follow government advice, such as social distancing, mask-wearing and isolation. Overall, these results illustrate the need to protect patients with dementia as part of the approaches used to control the pandemic.



Is antisense oligonucleotide gene therapy the way forward for treating Huntington's disease?

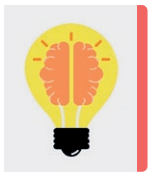
Maria Zareef Kahloon, Second-Year Neuroscience BSc Student at Queen Mary University London

Huntington's disease (HD) is an inherited neurodegenerative disease caused by a CAG extension in exon 1 of the huntingtin gene. An extended polyglutamine tract in the huntingtin protein is produced due to the expanded alleles, resulting in intracellular signalling defects. Antisense oligonucleotide (ASO) gene therapy is currently being pioneered to treat HD. In this therapy, oligonucleotides are inserted into cells and bind to the target huntingtin mRNA, inhibiting the formation of the huntingtin protein by either physically blocking the translation of mRNA or by utilising RNase H to degrade the mRNA. Previous ASO gene therapy experiments conducted on R6/2 mice that express the human huntingtin gene have been successful. The R6/2 mouse model is commonly used to replicate HD symptoms and is therefore useful for testing potential treatments. The transgenic R6/2 mouse has an N-terminally mutant Huntingtin gene with a CAG repeat expansion within exon 1.

In this successful experiment, scientists treated one group of R6/2 mice with the ASO treatment, which suppresses the production of human huntingtin mRNA, while saline solution was administered to the control group of mice. This experiment aimed to confirm if ASO therapy improves the survival rate in the R6/2 mice. The results showed that human huntingtin mRNA levels in the mice treated with ASO therapy were lower than in the control group. Furthermore, the mice treated with ASO therapy had a higher percentage of survival and lived longer than control mice. Thus, it could be concluded that if less human huntingtin mRNA was present in the ASO group, then less human huntingtin mRNA would be translated, and so there would be less synthesis of the huntingtin protein, compared to the control group.

The results of this study are enormously informative in understanding how gene therapy could be used to treat other neurological diseases. However, before ASO therapy is approved for clinical use, further trials will need to be conducted in humans to verify the same successful outcomes as in the R6/2 mice. If approved, then the symptoms of HD could be safely controlled with ASO therapy. Furthermore, scientists need to consider that an increased survival rate does not always correlate to an increased quality of life for the patient. Therefore, it needs to be established if the benefits of ASO gene therapy will outweigh the risks associated with it.

Furthermore, the drug PBT2 is currently being studied as a potential treatment option for HD. Some studies have inferred that the aggregation of mutant huntingtin proteins could be due to interactions with metals, including copper. Therefore, this drug is designed to lower extracellular metal levels and, consequently, decrease abnormal protein aggregations. This treatment has been shown to improve motor tasks and increase lifespan in R6/2 mice. However, as this treatment has a lot of shortcomings, further studies need to be conducted over a large period of time to confirm a successful outcome of this drug on HD patients.



Epilepsy and COVID-19: A potential link?

Laiba Ejaz, Second-Year BSc Neuroscience student at the University of Leicester

Epilepsy is a family of neurological disorders in which two or more unprovoked seizures or sudden rushes of electrical activity occur in the brain. Recent research suggests a potential link between epilepsy and COVID-19 via attenuation of the immune system and disruption of homeostasis of the brain.

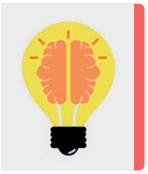
A theoretical link is important in science as it gives a foundation on which to base future research. Potentially, COVID-19 could lead to fever and/or weakening of the immune system, causing stress, lowering the seizure threshold and triggering a seizure. These epileptic seizures are triggered by a myriad of stimuli, as opposed to psychogenic seizures which are often physical manifestations of emotional stress. Exploration of the link between seizure onset and COVID-19 infection requires rigorous clinical assessments utilising both electrocardiogram and electroencephalogram monitoring to assess the plausibility of this hypothesis. At present, it is unclear whether patients will develop the recurring 'epileptic form' of a seizure following recovery from a COVID-19 infection, whether patients have isolated seizures, or whether those already prone to seizures experienced increased episode frequency when infected.

Clift and colleagues investigated the risk factors associated with COVID-19 hospital admissions. Their initial findings suggest a small increase in the risk of hospital admissions and death as a result of COVID-19, in both males and females with epilepsy. However, this does not prove that epilepsy was a direct cause for the reported higher risk. Being diagnosed with epilepsy may be associated with other factors that contribute to the risk of COVID-19 infection. For example, individuals diagnosed with epilepsy may have increased contact with healthcare workers or more frequently attend medical/educational settings. Moreover, patients with other underlying comorbidities might be more vulnerable to infection, exhibiting a higher rate of hospitalisation.

Firat and colleagues describe how older-generation anti-seizure drugs, such as carbamazepine, have a higher risk of drug interactions with medications used for treatment of moderate to severe

COVID-19. For instance, carbamezepine should not be used with the anti-COVID 19 therapy atazanavir (ATV). Co-administration might cause a clinically significant decrease in ATV concentration and an increase in concentration of carbamezepine, as a result of CYP3A4 inhibition. This could lead to increased drug exposure in the bloodstream and potential toxicity.

Further research into the underlying mechanisms, effects and treatment of COVID-19 may be an ongoing challenge for years to come. In particular, more studies are required to fully understand this potential relationship between COVID-19 infection and epilepsy. At present, there is insufficient evidence to suggest an immunocompromising effect of COVID-19 on epileptic patients or that seizures are worsened by contracting COVID-19.



Alcohol and the brain

Baraa Wahishi, Foundation Doctor at Warrington and Halton Teaching Hospitals NHS Foundation Trust

As a doctor working in a district general hospital in England, I find it staggering to observe how much alcohol permeates many aspects of people's health and lives, in a drastic manner. Alcohol has a historical place in both modern and ancient society, wherein its benefits have been celebrated while the harm it causes both to communities and individuals is often overlooked. In 2018/19, there were 358,000 hospital admissions related to drinking alcohol, and a further 1.3 million estimated admissions where the reason for admission or secondary diagnoses were linked to alcohol. Alcohol-related deaths hit a record high in 2020. Those who have experienced hangovers know that unpleasant sensation, but what exactly does alcohol do to our brain?

In lay terms, alcohol can be considered 'toxic', specifically, it can be neurotoxic, resulting in damage to (and often the death of) brain cells, as well as inflammation of the brain and body. Once ingested, alcohol is absorbed through the duodenum with some portion reaching the bloodstream in the stomach, after which it is pumped around the body, including to the brain. Some of this alcohol flows to the liver, where it is metabolised from toxic by-products (aldehydes) into H_2O and CO_2. To reach the brain, alcohol needs to cross the blood–brain barrier (BBB), a selective semi-permeable membrane, comprising endothelial cells that regulate the flow of substrates. Cells within the brain, including pericytes and astrocytes, connect these layers – allowing the BBB to maintain the integrity that is key to maintaining the brain's equilibrium (homeostasis).

At the molecular level, ethanol metabolites interact with cytoskeletal components to increase BBB permeability and initialise neuroinflammation, propagated by decreasing neural antioxidant activity and increasing oxidative stress responses. This is important given that the brain relies on a constant glucose supply to function adequately. If glucose supplies are gradually diminished (and not replaced) in neurons and glial cells, as in neurodegeneration, this has pronounced consequences. The disrupted equilibrium leads to neuronal toxicity and, often, neuronal death. Research into the effects of alcohol on the brain suggests a strong correlation between impaired glucose metabolism and neuronal loss due to alcohol-induced BBB dysfunction, resulting in neurodegeneration, which can impact cognitive function.

Neuroimaging techniques such as MRI can identify reductions in brain volume due to long-term alcohol use in individuals with chronic alcohol use disorders. The symptoms of these disorders are variable but can include motor dysfunction and mild to very severe cognitive deficits.

If alcohol is so harmful, why is it so pervasive? In part, the cultural celebration of its inhibitory effects and variable individual tolerance in group settings has played a part. At the individual level, the pleasant effects of this inhibition result from the activation of the brain's innate reward systems, providing a 'buzz'. This reward system promotes dopamine release in reward circuits, creating a reinforcing pleasurable feeling. Numerous neurotransmitters act on these pleasure circuits, which are thought to be involved in cognition and decision making. However, the brain, as in all things in life, works best in moderation.

COVID and the brain

Early epidemiological studies revealed that SARS-CoV-2 infections frequently affected the brain – the challenge now is to find out how.

When COVID-19 first appeared on the global public health radar early in 2020, most attention naturally focused on respiratory symptoms. For clinical researchers such as **Benedict Michael** (Liverpool), its potential impact on the brain was a further urgent question. Dr Michael, a consultant neurologist and MRC Clinician Scientist Fellow, was well aware of the potential of viral infections to affect the brain, following his work on the 2009 swine flu (H1N1) outbreak. "Back during the H1N1 pandemic, I helped lead the Association of British Neurologists' response. We did a national survey every month where every member of the ABN would receive an email that said 'have you seen a case of any of these neurological complications of H1N1?'."

Over two years, this surveillance network picked up 23 serious cases, mainly in children. When cases of COVID-19 began to pop up in places such as Italy and New York, Dr Michael dug out the H1N1 blueprint: "I said immediately to the team we should do exactly the same thing. Within days we were hearing cases of the odd stroke or the odd psychosis. It was clear it was not just neurological but across the brain–mind spectrum of neuroscience."

Casting the net wider

With a wide range of neuropsychiatric and neurological effects turning up, he made contact with the British Association of Stroke Physicians, the Royal College of Psychiatrists, and the Neuroanaesthesia and Critical Care Society. "I said, 'look were doing this surveillance study in adults in neurology, and we really think we ought to cover neuro-intensive care, neuropsychiatry and stroke, otherwise we could be missing potential complications. Why don't we come together and use all of our professional platforms to collect data?'."

By March 2020 the CoroNerve study had been approved, and by May 2020 data had been published in the *Lancet Psychiatry* on 153 cases – the first rigorous data on brain-related COVID-19 complications.

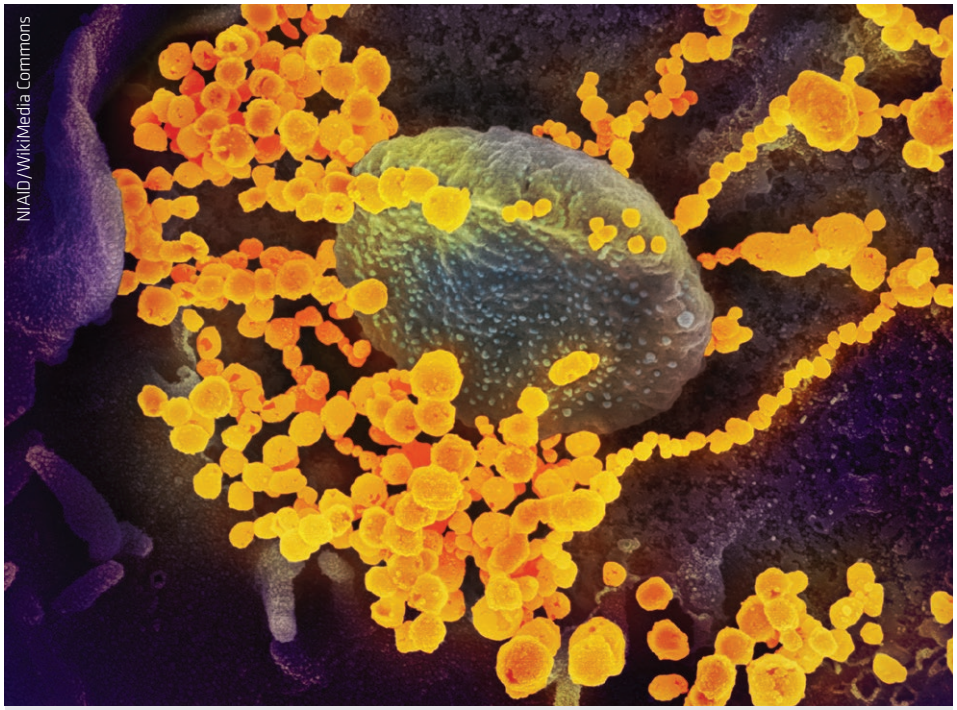
These early data suggested that, although affecting a minority of patients, brain-related complications were not uncommon and could have significant impacts: "What I learned from H1N1 was that if a sufficiently large denominator of people are infected, even rare complications become common. And that was clearly what was happening with SARS-CoV-2."

Furthermore, the complications could be life-changing: "For every 100 people hospitalised with COVID, there'll be 20 or so with some degree of brain dysfunction, and maybe 1–2% with a real brain disease. Although rare, they're important because potentially they're severe and disabling."

Stroke was the most frequent brain-related complication, but next common was alteration in mental status, says Dr Michael: "What was interesting was that within that group were diagnoses one would think of as 'neurological', such as encephalitis, but also diagnoses that would be typically thought of as 'psychiatric', such as psychosis, catatonia and mania, and those diagnoses were disproportionately affecting younger people. About half of them occurred in people under 60, and a quarter of them occurred in people in their 20s, 30s and 40s."

Benedict Michael

Over the next year or so, the collaboration has gathered data on nearly 1000 patients, and undertaken an in-depth assessment of around 250. This revealed that strokes were particularly common in those with a range of modifiable risk factors, such as high blood pressure,



NIAID/WikiMedia Commons

SARS-CoV-2 emerging from the surface of cells.

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"FOR EVERY 100 PEOPLE HOSPITALISED WITH COVID, THERE'LL BE 20 OR SO WITH SOME DEGREE OF BRAIN DYSFUNCTION, AND MAYBE 1–2% WITH A REAL BRAIN DISEASE. ALTHOUGH RARE, THEY'RE IMPORTANT BECAUSE POTENTIALLY THEY'RE SEVERE AND DISABLING."

type 2 diabetes and atrial fibrillation. "Clearly, there's a huge public health implication here for a pandemic that's not going anywhere soon in most of the world."

Infections are known to increase the risk of stroke in older patients. "In younger people who are having a stroke ahead of time," suggests Dr Michael, "the hypothesis is that some combination of hypertension, hypercholesterolaemia and diabetes results in atherosclerosis, and that this vasculature is therefore 'primed' to respond adversely to an endotheliopathy caused by SARS-CoV-2."

Disease mechanisms

With **Gerome Breen** (KCL), Dr Michael is now leading another nation-wide collaboration, COVID-CNS, to explore the mechanisms underlying these brain-related complications. The team is recruiting 800 hospitalised COVID-19 patients with neurological and/or neuropsychiatric symptoms alongside 500 matched controls. "We're doing a really detailed clinical work up, their neurology, their psychiatry and their cognition, all worked up face-to-face."

Professor Breen is leading studies aiming to identify genetic factors predisposing to brain-related complications. H1N1 again may hold lessons – multiple cases of acute necrotizing encephalopathy were linked to mutations in the *RANBP2α* gene, which encodes a component of the nuclear pore complex. The COVID-CNS team is also analysing viral strains, cytokines, chemokines and autoantibodies directed against the brain to identify factors associated with severe brain disease.

Initially, there were some suggestions that SARS-CoV-2 might be infecting brain tissue, perhaps via the olfactory nerve given its effects on the sense of smell. Infection of brain cells now seems unlikely – the virus probably only infects cells of the blood vessel wall. Rather, infection probably leads to a breakdown in the blood–brain barrier, allowing the influx of inflammatory mediators and immune cells. "We're now looking at the immune response that is driving that breakdown in blood–brain barrier integrity," says Dr Michael.

SARS-CoV-2 is notable for the range of brain-related complications it can cause. Post-infectious demyelination and brain inflammation were not unexpected, says Dr Michael. "What has been unusual is its ability to affect cerebral vasculature, and in such high numbers." It is likely that a range of pathogenic pathways may be involved – some cases of psychosis, for example, have been linked to autoantibodies targeting the NMDA receptor or are associated with autoimmune encephalitis.

SARS-CoV-2 infections are also associated with long-term impacts on health – long COVID. However, this is likely to be a highly heterogeneous condition, so COVID-CNS is concentrating on hospitalised patients: "When you want to get at underlying biological disease mechanisms, it does help to focus on the severe hospitalised phenotype to get a really tight handle on the biology."

Complementing these clinical studies, Dr Michael has developed a mouse model that better reflects clinical presentations: "There's a temptation as soon as a new pathogen arrives to immediately investigate it in an animal model. But I really think we need to take a reverse translational approach and understand the clinical phenotype and associated biomarkers, and to develop models that reflect that."

Viral encephalitis

Before COVID-19 broke, Dr Michael was using models to explore the mechanisms of viral encephalitis – and he has managed to keep such research going despite the demands of the pandemic.

While in Boston, USA, Dr Michael used microscopic neurosurgery to remove portions of the skull of mice, replacing them with glass. He was then able to use lasers to image white cell migration in the brain in real time, focusing on herpes simplex virus (HSV) infection.

These studies revealed a critical role for neutrophil infiltration into the brain. Furthermore, the chemokine CXCL1, released by neurons and astrocytes, was the critical driver of this infiltration: "If we blocked that, either by using a blocking antibody or by using mice that lacked the receptor, we could completely abrogate the capacity of neutrophils to get into the brain even in the context of active viral infection. In so doing, we could maintain the integrity of the blood–brain barrier, so those mice would survive."

Late in 2020, Dr Michael was awarded an MRC Clinician Scientist Fellowship to take forward this work. The aim is to use mouse models to understand in more detail the signalling pathways associated with CXCL1, and those that are activated when it is inhibited, to identify the most promising target for intervention development.

"We need to understand that whole pathway, from neuronal infection all the way to the blood–brain barrier, so we can work out where along that pathway we need to block to treat patients," says Dr Michael. He also stresses the wider importance of such studies: "Understanding HSV encephalitis has translational implications for all the other different viruses that cause encephalitis, which currently have no treatment whatsoever."

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MAPping the course of dementia

Multi-omics technologies could provide new insights into the causes and progression of Alzheimer's disease.

Alzheimer's disease remains stubbornly resistant to the development of effective therapeutics, with drug development failure rates depressingly high. In large part, this reflects an incomplete understanding of the molecular mechanisms of disease, and the links between the pathology observed and cognitive symptoms. At Imperial, **Jo Jackson** is leading a UK Dementia Research Institute (UK DRI) initiative that is using a variety of 'omics' technologies to characterise the molecular changes occurring through disease progression, alongside her own research on degeneration of the synapse.

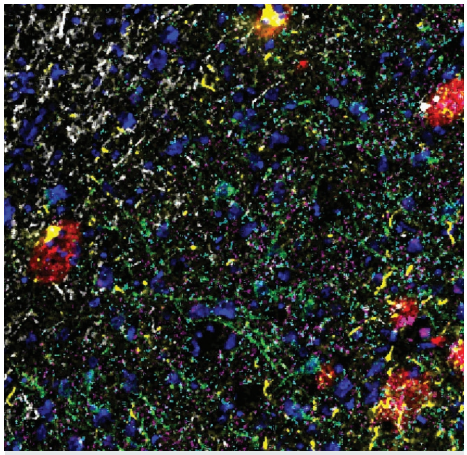
After a PhD at Imperial and postdocs at Lund in Sweden and back at Imperial, Dr Jackson had the opportunity to set up a two-photon imaging facility at Eli Lilly. She soon became a permanent employee, running a research programme focused primarily on the role of synapse loss in Alzheimer's disease.

In 2019, she decided to move back to academia, taking up her current position at Imperial, which combines leadership of the UK DRI's Multi-omics Atlas Project (MAP) and research on the synapse.

MAPping AD

MAP is a £2m UK DRI Director's initiative. "The idea is to comprehensively characterise the pathology of human Alzheimer's post-mortem brain tissue," says Dr Jackson. Of course, plenty of work has been carried out on Alzheimer's disease pathology, but the MAP initiative differs from past efforts in several significant ways.

The first novel aspect is the range of molecular technologies that are being applied to characterise tissue samples. These include epigenetic, transcriptomic, proteomic and lipidomic analyses, providing a wealth of insights into epigenetic tags on DNA, messenger RNAs and gene expression, proteins, and lipids.



Imaging mass cytometry allows the visualisation of multiple markers on one tissue section. Here, a panel of seven antibodies has been used to visualise pathology, cytoarchitecture, axons, dendrites and synapses. Image courtesy Sulin Liu.

"Each piece of data is traceable back to the donor brain," points out Dr Jackson, "but more importantly to the specific region of that brain." The project is focusing on eight different regions of the brain affected at different stages of Alzheimer's disease, breadth of coverage that again marks MAP out from previous projects.

The goal is to trace the molecular progression of Alzheimer's disease, says Dr Jackson. "We're interested in the early stages so we can determine the molecular tipping points of the disease and the pathology. That is difficult – people usually die at the latest stages." However, looking at brain regions affected at different stages should provide some insights into disease progression. "Because we have the eight different brain regions, it means we can create a pseudo-temporal profile of the disease – we know different brain regions are affected at different stages of disease."

In addition, some donated brains are at a mid-stage of disease progression, while some control brains, which are undergoing similar intensive analysis, also show early signs of Alzheimer's pathology.

The initiative is a massive data-management challenge, with analyses being run on ten samples from eight regions in 12 Alzheimer's disease and six control brains. "When you start multiplying those numbers up, that's quite a lot of brain tissue," points out Dr Jackson.

Furthermore, each omics approach actually involves multiple technologies. The transcriptomics analysis, for example, includes both single nuclear transcriptomics and bulk transcriptomics, but there is also growing interest in 'spatial transcriptomics' – analysis of mRNAs within specific compartments of the cell.

Dr Jackson co-chaired a seminar at BNA*2021*: Festival of Neuroscience on single-cell approaches. "One of the things that came out of that session was the opportunity to look at spatial omics, in particular transcriptomics. The field is moving really fast in this space."

Studies have shown that mRNA transcripts in dendrites, axons and cell bodies can be very different, and spatial resolution is continually improving. The Imperial team is collaborating with US researchers at the Broad Institute, who have developed a high-resolution approach known as 'slide-seq'. "It's an emerging field, but it's very important to look at the localisation of these transcripts and their spatial relationship with the pathological hallmarks of the disease."

A key responsibility of Dr Jackson and her team is to create a pipeline and platform that can assimilate huge quantities of data, make sense of it, and make sure it is available for others to work with. "We're very keen on this being an open-science platform to benefit the field as a whole."

The team has been gearing up for large-scale analysis of MAP samples by

Johanna Jackson, who runs the UK DRI's Multi-omics Atlas Project (MAP).

characterising existing tissue collections. Most advanced is a multi-omic analysis of tissue samples from carriers of *TREM2* mutations, one of the most significant risk factors for Alzheimer's disease. *TREM2* codes for a receptor found on myeloid cells, highlighting the potentially key role of immune responses in the condition.

Focus on the synapse

Alongside work on the MAP initiative, Dr Jackson is also studying synaptic changes in Alzheimer's disease, taking her past research in new directions. "Up until I joined the UK DRI, I'd done all my previous work in pre-clinical models, in transgenic mouse lines. I'm now essentially moving that into human tissue."

Her interests include how synapses are affected as pathology progresses, including differences between pre- and post-synaptic components and excitatory versus inhibitory synapses.

Recent years have seen great efforts made in understanding and targeting underlying disease mechanisms, such as the build up of beta-amyloid plaques and spread of tau pathology. Dr Jackson suggests that focusing on synapses is a valuable complementary strategy: "Everyone associates Alzheimer's disease with cognitive impairment, and what leads to cognitive impairment is the loss of synapses."

Synapse loss might be directly attributed to Alzheimer's disease pathology or a consequence of other mechanisms such as inflammation. Either way, interfering with underlying pathology may not be sufficient to address all symptoms: "Even if you can stop the disease in its tracks, patients will still have some cognitive impairment because some synapses will have been lost." She envisages that some form of combination therapy might ultimately be possible: "Ideally, if you give a disease-modifying therapy with a therapy that targets synapses, you might be able to not only stop disease progression but also restore or at least halt the changes in cognitive impairment."

As well as work with post-mortem samples, she also hopes to expand into other models of human disease, including induced pluripotent stem cells and organoids. She is also collaborating with researchers at McGill University in Canada to characterise live resected tissue obtained during brain surgery. Initially, the aim will be to check the difference in tissue quality between post-mortem and live tissue to understand the effects of sample preservation techniques on the data generated.

She is also building on her experience of imaging. She is introducing the CLARITY platform, which renders brain tissue transparent, as well as imaging mass cytometry. "The main advantage of this is that you can use up to 37 markers on the same tissue section," she explains – a big improvement on current techniques, which can visualise only a few markers at a time.

"THE EXPERTISE THAT IS AVAILABLE ACROSS THE UK DRI IS VAST AND EVERYONE IS OPEN TO SHARING AND COLLABORATING. BASED ON HOW COMPLICATED ALZHEIMER'S IS, THAT'S THE APPROACH WE NEED TO TAKE."

A virtual institute

UK DRI is an innovative venture, spanning some 600 researchers at sites across the UK. "The expertise that is available across the UK DRI is vast," says Dr Jackson, "and everyone is open to sharing and collaborating. Based on how complicated Alzheimer's is, that's the approach we need to take."

A wide range of cross-centre initiatives have been established. For example, researchers in particular themes, such as the synapse and bioinformatics, interact regularly and share their differing perspectives. "It works well and you get to know people from other centres really well because you work closely with them."

Collaborations have also been established with industry, for example through joint postdocs. "There's a few of those now," says Dr Jackson. "I think industry are very much open to this model, and to getting these collaborations going."

Her own time in industry, she suggests, has been extremely valuable in her new role. "One of the things you learn to do in industry is manage these larger-scale projects. That set me up quite well for leading this project at the UK DRI."

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A deep dive into the seal brain

Brain imaging of seals could reveal more about how they are affected by environmental disruption.

Seals are expert divers, with physiological adaptations that enable them to forage underwater for hours. Over the past two decades, however, significant new human activity has begun to impinge on their natural environment, as renewable energy installations such as windfarms are constructed. At the Sea Mammal Research Unit at the University of St Andrews, **Chris McKnight** has turned to non-invasive brain imaging to determine how these activities might be affecting seal sensory perception, behaviour and survival.

Decarbonisation of energy generation has led to increasing investment in green energy schemes, including windfarms and tidal turbines. Essential though such activities are, one unwanted side effect may be impacts on marine animals. Windfarm construction, for example, involves extensive pile-driving activities, generating noise and pressure changes that could impose a cost on sea mammals such as seals. "At the moment we don't have a way of accurately estimating what that cost is," says Dr McKnight.

Sensory ecology

The sensory systems of seals are well adapted to their environment and lifestyle. They have good eyesight and hearing, and sensitive whiskers that can detect water movements. These are used to guide behavioural responses that spans long-distant swimming to sites where prey may be found, location of schools of fish, and their capture. "We have no idea how those are systematically put together," says Dr McKnight.

Activities such as pile-driving add new, alien sensory inputs: "They're incredibly loud," he points out. "How does that change the sensory landscape?"

It remains unclear whether and how seals perceive these sonic intrusions, how they respond physiologically, and whether they adapt or habituate. Some behavioural analyses with tracking data have been made, which have revealed that seals sometimes vacate sites where pile-driving is taking place and sometimes stay put. "And we have no idea why there is such variability," says Dr McKnight.

Turning to NIRS

Keen to understand more, Dr McKnight began to explore the opportunities offered by near-infrared spectroscopy (NIRS). A non-invasive imaging technology, NIRS can detect changes in oxygen binding to haemoglobin and has been used to infer levels of brain activity, including regional variation (functional NIRS, fNIRS).

PHYSIOLOGICAL CHANGES DIFFER SIGNIFICANTLY BETWEEN SHORT AND LONG DIVES – THE ANIMALS' HEART RATE MIGHT DROP TO 40 BEATS PER MINUTE ON A SHORT DIVE BUT TO AS FEW AS 4 BEATS PER MINUTE ON A LONG DIVE.

Initially, the challenge was to adapt the NIRS for use with a marine mammal. A company manufacturing wearable NIRS equipment was willing to supply the technology, but it was down to Dr McKnight and his colleagues at St Andrews to make it work with seals.

Fortunately, his unit has a section specialising in this kind of challenge: "They develop a whole suite of underwater systems for application on a variety of animals – sharks, turtles and penguins, but mostly diving animals, seals and sea lions."

The instrumentation team, led by Steve Balfour, was able to create devices that were water-proof, pressure-proof and also seal-proof – "They're not very delicate animals," points out Dr McKnight.

As well as these technical challenges, he also had to consider the specifics of seal anatomy and physiology. "They have interesting neurophysiology," he points out. "They have redistributed nearly all of their cytochrome c and neuroglobin out of the neuron and into the astrocyte." Neuroglobin is a high-affinity oxygen-binding molecule that helps to protect neurons and the brain from hypoxia. It is normally found in neurons but for some reason in seals it is found solely in astrocytes.

To find out why, Dr McKnight contacted researchers, including the discoverer of neuroglobin, Hans Burmester – to no avail: "They have no idea why they would do that."

Another key challenge was disentangling NIRS data relating to brain

Magnus Johansson/WikiMedia Commons

A grey seal, one of two UK seal species.

A human free diver in action.

responses and physiological responses, where again seals show some remarkable adaptations. "They can go from 120 beats a minute to 4 beats a minute within a couple of beats," says McKnight, leading to dramatic changes in blood O_2 and CO_2 levels. These fluctuations generate noise that presents a significant data-processing challenge – far harder than for humans who, in general, are regular breathers with fairly steady heart rates.

As well as instrumentation experts, St Andrews also has the advantage of a large test facility in which pseudo-real world experiments can be carried. This includes a deep pool allowing animals to dive to reach a platform on which food can be provided.

Preparing to dive

The St Andrews team has discovered some remarkable aspects of physiological control in seals. Although the animals spend a lot of time diving, 80% of dives last less than two minutes. Physiological changes differ significantly between short and long dives – the animals' heart rate might drop to 40 beats per minute on a short dive but to as few as 4 beats per minute on a long dive.

Remarkably, it appears that this is not a wholly autonomic response to a dive but involves active preparation by the seal. "Bizarrely, there's some hack over the autonomic system," says Dr McKnight. "They set themselves up in advance for the anticipated challenge of the next dive, sometimes starting as long as 40 seconds before submersion. It makes sense but we're not sure how they achieve it."

This highlights the importance of understanding how they are being affected by sensory disturbance caused by pile-driving. "When they're disturbed, they do tend to drop much deeper," says Dr McKnight. If they have not prepared beforehand, this deeper and longer dive could have harmful consequences – as seen in deep-diving species such as toothed whales, which can result in mass stranding events.

Seal senses

Extending this work with the fNIRS equipment, Dr McKnight first needed to check that meaningful results could be obtained, using passive sensory stimuli in their experimental pool. "We had some idea where we would expect regional responses for the different stimuli, based on old, historical quite invasive work," he says. "We brought a small group of juvenile grey seals into the pool, presented them with the different stimuli, and then went through the usual fNIRS processing pipeline to attempt to get to the situation where we could see significant haemodynamic changes associated with each sensory stimuli."

Reassuringly, the results did seem to match expectations: "Ultimately, the bottom line is you can get at the haemodynamic response and you get some regional differentiation."

Dr McKnight is keen to move beyond the pool: "Ultimately we want to start doing it in the wild." Whole-brain multisensory recordings may be too ambitious at this point so the initial focus is likely to be on sound perception. "Auditory sensing in a marine environment is a great one to do because sound propagates so well," says Dr McKnight. Sound signals are also relatively easy to capture, he adds, "So we have a good idea of the acoustic landscape around the animal." A key goal will be to integrate this information with that from other data-loggers, for example those that track the animal's orientation and movement, which can be used to infer behaviours such as foraging and capture of fish.

Deep diving

Unexpectedly, Dr McKnight also found himself studying elite free divers, following contact made by free-diving researchers in Sweden. This led him to wild-water NIRS studies with people like Alexey Molchanov, a free-diving world record holder from Russia.

"That was my first day out," recalls Dr McKnight who monitored responses as Alexey spent three and a half minutes on a deep dive: "I was in the boat having absolute kittens."

The recordings illustrate the remarkable physiological changes deep divers undergo, and their uncanny ability to maintain some degree of cognitive control over them. He now has plans to extend this work to indigenous diving populations, such as those in Tonga, who show evolutionary adaptions to deep diving and are more cavalier in their approach to diving.

Back in Scotland, he hopes that his work will shed light on the brain responses of seals so that their behaviour can be better understood, particularly their responses to environmental noise and other disturbance. This could have real practical relevance for harbour seal ecology: "Overall around the UK population numbers are doing well, but in Scotland, particularly the east coast here and Orkney, the numbers are incredibly poor."

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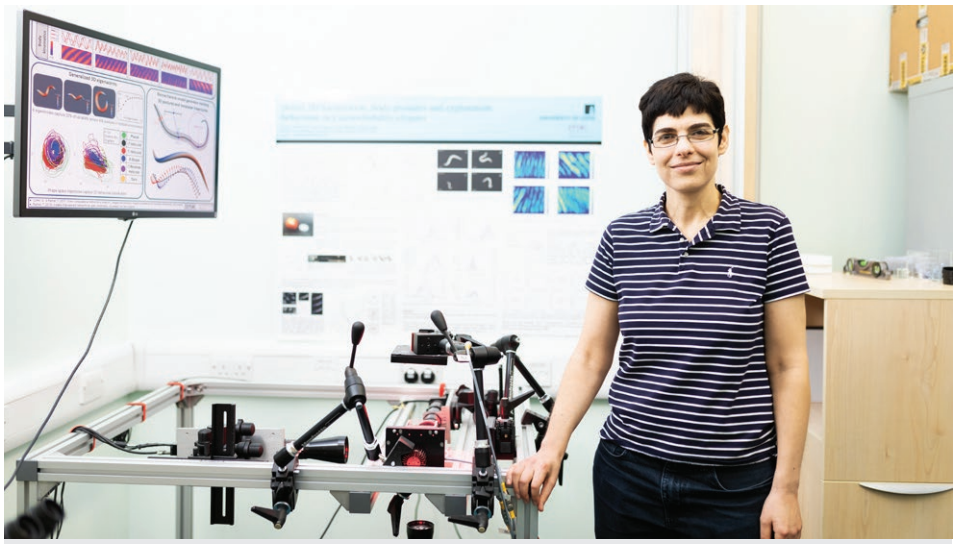
Neuroscience's hydrogen atom

A physical science perspective is providing new insights into the brain of a worm.



Netta Cohen, with the apparatus used to capture 3D images of nematode worm locomotion.

A glance at her active grants gives some clue to the eclectic research interests of **Netta Cohen** (Leeds). Alongside studies on the locomotion and sensory systems of the nematode worm *C. elegans*, her other work covers self-repairing cities, plant root growth and 'pipebots' – miniaturised robots designed to work in underground pipe networks.

These wide-ranging interests were apparent early, with Professor Cohen seeking out a broad-based undergraduate education in the USA, before opting to specialise in physics: "Physics seemed appealing as it's very mechanistic – you understand where things are coming from, and it's very beautiful: there are these elegant theories that bring things together, and it's a good foundation for virtually anything."

Having initially begun studying quantum optics, she chanced upon a new biological physics lab and began a PhD there instead: "So I started working in a biology lab in a physics department."

At this point, physics was the driver of her studies: "The questions we were asking were physics questions, and the biological system was just a system that could offer a way to answer questions that couldn't be answered by studying, say, metals or gases."

For a physicist, she suggests, a living thing is simply a (very) complex system: "Nevertheless, there's something about a biological system that's different and really intriguing to physicists, and has been for centuries," she adds. In particular, living systems appear to defy the second law of thermodynamics, refusing to become more disordered over time. This is intimately related to living systems being in a state of non-equilibrium. "Physicists are fascinated by non-equilibrium systems," says Professor Cohen. "We don't know what to make of them – we don't have a general theory to deal with them, instead tackling them on a case-by-case basis."

She points out another attractive feature: "Biological systems are not as simple as standard solids and liquids and gases. In order to achieve their function, they have to be built out of simple components, but those components have to communicate across scales to control the system as a whole, otherwise it all falls apart."

Biological systems

Professor Cohen therefore cast around for a biological system on which to work: "I was really interested in neuroscience from the very beginning, but I was scared because neurons are so complicated..."

Instead, she settled on contractile heart cells and how they form collectives that beat in unison. Starting with individual units, she began to investigate how rhythms emerge in heart cells and which features of individual heart cells scale up to the network level (or, conversely, which aspects of the network scale down to the single-cell level). "That's a physicist's way of asking questions about a biological system," she notes.

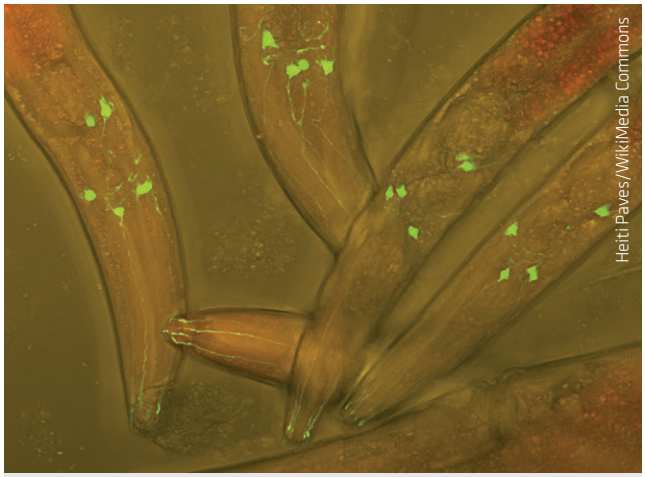
Another advantage of biological systems is that, unlike metals, they have a clear purpose: "It's really easy to understand what the heart is supposed to do – the heart is supposed to pump." The insights gained about the properties of components and networks can therefore be placed in this functional context.

Furthermore, left alone, metals tend not to do much, but biological systems are ever-changing. Having constructed an incubator for her heart cells, Professor Cohen was able to monitor their behaviour over days, gathering data on rhythmic and arrhythmic dynamics acting over very different timescales.

Given the focus on physics, she ended up publishing her results in physics journals: "That frustrated me. I wanted to know whether the insights we gained were biologically relevant or not." She realised this would require her to expand her horizons still further: "I decided I really needed to spend some time with biologists."

Hail the worm

She found a position in a multidisciplinary research environment that combined mathematical biology, neurobiology, physics and molecular evolution: "I split my time between four different labs to try to absorb as much as I could." She got her first taste of neuroscience, exploring the activity of cortical cultures and a central pattern-generating system in the locust



C. elegans with GFP-stained neurons.

"THERE'S SOMETHING ABOUT A BIOLOGICAL SYSTEM THAT'S DIFFERENT AND REALLY INTRIGUING TO PHYSICISTS, AND HAS BEEN FOR CENTURIES."

nervous system.

She felt she was going in the right direction, but something was still missing: "Then I arrived in Leeds and discovered *C. elegans*."

Sydney Brenner had selected the nematode worm as a potentially solvable biological puzzle in the 1970s. "*C. elegans* is great," says Professor Cohen. "It has 302 neurons and they're mapped. It's accessible, it's tractable – it's what a physicist would call the hydrogen atom of animals."

She set about identifying a question she could address: "Thinking like a physicist, I said, 'this is a system I don't know very well, what can I start with that's simple?'." Worm locomotion seemed perfect, particularly given the distinctive sine wave animals trace out as they move: "Sine waves I understand – I'm a physicist: this I can deal with."

Moreover, biologically, movement is central to the worm's existence: "Locomotion is absolutely essential for everything it does. It doesn't have arms in order to write a letter or play chess, it doesn't have a tongue to speak with. All it can basically do is go from A to B."

Although the nematode worm is not segmented, its muscles and associated neural connections show a modular arrangement along its length. "So you can think of it in terms of repeating units and coupling of units," says Professor Cohen, who went on to develop models that capture the synchronisation of these units to achieve coordinated sinusoidal locomotion.

Taking control

Moving on, she and her group began to explore the sensory-motor control of locomotion – how does the worm make decisions about movement in response to a dynamic environment?

With colleagues in The Netherlands, Professor Cohen and her group developed a computational model to explain a worm's response to salt. The model suggested that sensory cells do not simply convey messages on salt levels to a brain centre for processing. Instead, they are part of neural circuits that show considerable plasticity in their response to different salt concentrations. The point, suggests Professor Cohen, is that worms do not need to know precise millimolar concentrations of salt – from a worm's point of view, changes in concentration are more important: "Ultimately, what an animal needs to know is, 'am I going in the right direction?'."

Whether a particular salt level is good or bad therefore depends on context. More complex brains can interpret sensory information to take account of context, but as *C. elegans* has so few neurons to play with, the sensory cell itself is contributing to these computations: "It's not two or three synapses down, it's right there. The sensor actually turns itself off."

This computational modelling also led to a further fruitful collaboration with a group from Yale, led by Michael Nitabach. The US team had been exploring decision-making, placing an attractive odorant outside a ring of toxin surrounding the animals and monitoring whether and when the worms made a bolt for the treat. Professor Cohen and her group were drafted in to develop models of the experimental findings: "And within a few days we had some results."

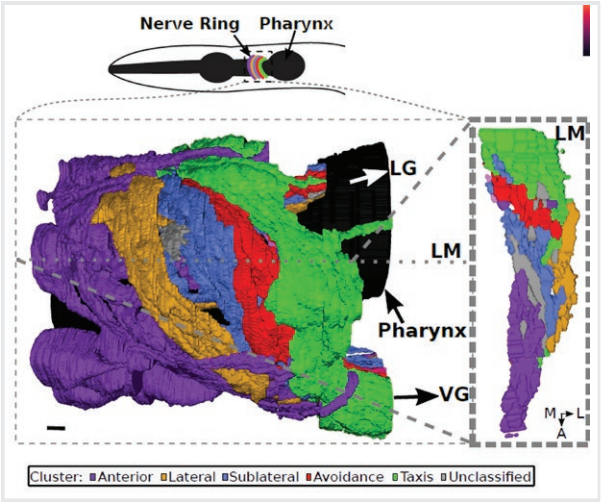
The scenario creates a decision-making dilemma for the worm. If it stays put, it risks dying of starvation; if it heads for the attractant, it runs the risk of being poisoned. Over time, the latter risk drops, as the toxin begins to diffuse away.

Using molecular biology, the Yale researchers had identified the key worm cells involved in decision-making, but needed someone to determine the computation performed to control the behaviour. Professor Cohen showed that two mechanisms – one based on a threshold and the other on coincidence detection – could account for the data. "The power of a good model is the ability to make predictions that would allow different models to be disambiguated," she explains. "The way we designed the experiments exploited our knowledge that risk aversion was hunger dependent, so we would measure the effects of food deprivation to choose between two model frameworks, the coincidence detector and the threshold. It turned out the simpler, threshold-based mechanism explained the data better."

Making connections

Recently, Professor Cohen has become involved in the growing field of connectomics, after Christopher Brittin joined her group. With a background in maths and physics, he had been working in a US connectomics lab, where he had derived the first volumetric data set of the worm's brain (actually, of two worm brains). Each neuron, synapse and gap junction in the head region of the worm was now assigned a physical location.

"We spent hours and hours discussing what we can do with this data set," says Professor Cohen. She was becoming increasingly interested in how locomotion was being controlled and the steps between sensory detection and movement. Yet worm connectomics didn't seem capable of answering that question: "The connections run in all directions – you can't see a thing. How are you going to understand what the brain is actually doing?"



The layers of the nerve ring.

"THESE ANIMALS, JUST LIKE ALL OTHER ANIMALS, HAVE INDIVIDUALITY, THEY HAVE VARIABILITY – THEY'RE NOT ALL THE SAME. THAT VARIABILITY IS CONSTRAINED BY THE SPATIAL CONNECTOME."

Professor Cohen and Dr Brittin began to apply their statistical skills to unpack the challenge: "One of the problems we had was that we only had these two animals, and there was a lot that wasn't the same between these two animals. And there were many connections that differed between the left side and the right side of their largely bilaterally symmetrical brains. There was way too much noise."

With two animals, divided into their left and right sides, they assembled four data sets. They began to compare which neurons were in physical contact and which were synaptically connected, and developed statistical models to explore how often particular neurons were connected in the four data sets: "All of a sudden everything fell into place."

The statistical analysis revealed that, although there is a conserved core set of neural connections, many others are variable between animals. "These animals, just like all other animals, have individuality, they have variability – they're not all the same." Importantly, spatial organisation limits what connections can be made: "That variability is constrained by the spatial connectome – the 'contactome'."

This has serious implications, says Professor Cohen: "As far as I know that's completely overturning the thinking about *C. elegans*." It has been assumed that the worm connectome is conserved, but in reality that may be true of only about half of its connections.

The analysis also revealed unsuspected order in the bowl of neural spaghetti in the animal's main neuropil (or brain), known as the nerve ring. "We have these five layers of cells that tend to be more tightly connected to each other than across layers. So there's a physical organisation to the nerve ring that is ordered from anterior to posterior."

On top of this, integration with the functional properties of neurons begins to offer clues to the nerve ring's modus operandi. The standard model of brain function involves an information pipeline: sensory signalling to the brain, central processing, and then action signals. However, Professor Cohen suggests that integration functions must have a more pivotal position in the wiring diagram: "It all needs to communicate, it all needs to be coordinated. The animal has to function as a single animal not as five clusters of animals." Her model puts sensors at the top, and integration and coordination at the bottom: "That now gives you a very beautiful brain map."

Although intellectually satisfying, Professor Cohen is aware that the analysis is a beginning not an end: "The question is, what can you learn from that map, is it real? And again I don't know. That's future work."

Future directions

As well as pursuing leads from the connectomics research, Professor Cohen and her group are also continuing to explore locomotion: "The animal doesn't just do sine waves," she points out. "We love to think of it as living on a Petri dish, but it doesn't ecologically." In particular, in its native soil and compost heaps, the worm moves about in three-dimensional space. Professor Cohen and colleagues have devised a sophisticated 3D imaging platform that manages to combine high resolution with significant depth of field. Her work now is focused on developing computational models of the 3D patterns of movement observed and their neural control.

She is also applying what she has learned from biology to the design of robots. The worm's neural computations, she suggests, could be useful in an engineering context. Although the approach has its limitations – "I wouldn't use a worm's nervous system to fly an aeroplane," she suggests – one application currently being explored is in the control of a swarm of low-cost autonomous robots that monitor urban roads for signs of wear and tear (see **www.youtube.com/watch?v=2avPQxqMC58**). "It spends the night roaming the streets and it can find cracks much better than any benchmark we've tested it against."

She is also contributing to a major 'pipebots' programme, which is developing micro-robots designed to operate in underground and inaccessible pipe networks.

The humble worm is thus providing exciting possibilities for both discovery and application: "It's opening up a huge number of questions about the application of neural architectures and algorithms to engineering."

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Summing up neuroscience

Grace Lindsay has taken time out from research to pen a paean to maths in neuroscience.

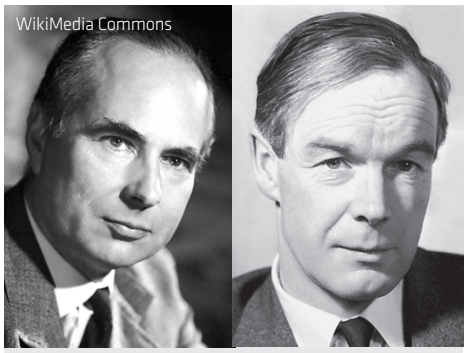
Mathematical equations are a key tool of the trade in **Grace Lindsay's** day job as a computational neuroscientist at UCL's Sainsbury Wellcome Centre. Despite the increasing centrality of mathematical approaches in neuroscience, however, she felt that popular books were not giving it due attention: "I didn't feel that was fair to people who were interested in the brain," she says.

Her interest in computational approaches harks back to a departmental seminar during her undergraduate days: "I went to a talk by a professor who was doing mathematical neuroscience, and I found it more interesting than I expected and more satisfying than I expected."

She admits that she held misconceptions about what computational neuroscience actually was. "Prior to that, I thought I didn't like the computational side of neuroscience; I thought it didn't make sense to think of the brain as a computer." The talk, on dynamical systems modelling, made her realise its scope was much broader: "I thought 'oh, that feels right, that is what the brain is'. I didn't realise that there were mathematical tools that would let us get a hold of things and make certain complicated problems more tractable."

Always keen on writing, she set up a blog and later a podcast. In 2019, she went a step further, starting work on a popular science book on mathematical approaches in neuroscience. In part, her goal was to raise awareness of this increasingly critical part of neuroscience: "The mathematical side of neuroscience, despite the fact that it's growing within neuroscience itself, the public never gets to see that."

A second goal was to provide an account of the origins of the field: "Computational neuroscience itself didn't have a real history that it could point to," she notes. The task involved many hours of deskwork, tracing the development of the field, landmark papers and the key individuals. "I think it's super-interesting to see what happens when people cross disciplinary boundaries, and that's what the whole history of computational neuroscience is."



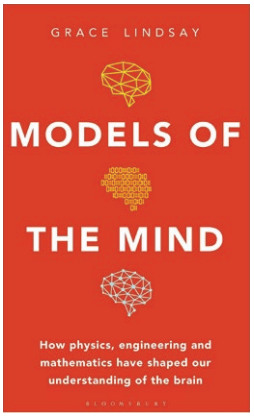
Andrew Huxley (left) and Alan Hodgkin, pioneers in the application of maths to understand action potentials.

She examines multiple ways in which mathematical approaches have illuminated the function of the brain and nervous system. "Each chapter focuses on a different subject in neuroscience, starting with individual neurons, all the way up through groups of neurons to behaviour, and the mathematical approaches that have gone along with studying those things. Each chapter in itself is a story."

The book highlights how diverse the field is: "I wanted to showcase the breadth of math that's used to study the brain," she says. "We use it all – we use what works the best for the level of the brain you're studying and what questions you have."

Recent years have seen fruitful dialogue between computational neuroscience and the field of artificial intelligence (AI), particularly with the development of biologically inspired neural networks capable of increasingly sophisticated feats. "On the flipside, neuroscientists such as myself are using artificial neural networks as models of the brain to think about how the brain works."

However, despite this recent convergence, AI and neuroscience have distinct goals: "AI just wants to make a model that's useful for their purposes and we want one that looks like the brain. I anticipate there will be another splitting of these two fields for a bit before they merge again."



This focus on AI also begins to encroach on more philosophical questions such as the nature of consciousness. While aspects of consciousness can be studied mathematically, Grace suggests, the subjective experience of consciousness is not something that maths can address. "My stance is it seems scientifically out of reach, at least at the moment."

A take-home message from the book is the centrality of mathematics: "The general thrust, and I try to make this emerge in each chapter, is that we will need mathematical modelling to understand the brain – it's just too complex, there's too much going on." How the brain works, she argues, cannot be rigorously described with words alone: "You need to write it down explicitly in equations."

A second key point is that modelling necessarily involves simplification, a focus on the core of a question: "That process is subjective. When you're building a model you're not trying to perfectly replicate a thing." Rather, the goal is to extract its essence, to concentrate on what really matters: "Modelling is an art and a science."

• ***Models of the Mind***: *How physics, engineering and mathematics have shaped our understanding of the brain* is published by Bloomsbury Sigma.

From hellraiser to trailblazer

After a tempestuous adolescence, a love affair with science has motivated **Karen Duff** to research success.

In 2019, Karen Duff returned to the UK from the USA to head up the UK Dementia Research Institute's (UK DRI's) centre at UCL. Having been born and bred in London, it was a return to her roots after more than 25 years living abroad. Although now a scientific leader and part of the UK scientific establishment, her early career was not without its ups and downs.

Medicine was a part of her life from an early age – her father was an ENT surgeon and her mother a nurse. However, her father had no part of her life beyond the age of 3. At an A-level college providing little by way of discipline, she indulged in her love of music (punk rock was an early influence), left home at 16, slept in late – and flunked her A-levels.

"I had a rather difficult time during my teenage years," she recalls. "I wasn't a stellar student at all. I got DFF, which shocked me greatly."

After a crammer course and retakes, she sought out a university that placed more emphasis on interviews than grades, landing on the University of East Anglia (UEA). Here, her genuine passion for genetics – inspired by a sixth-form lecture – shone through and she was offered a place.

"UEA ticked all the boxes," Karen says. "The university was surrounded by 365 pubs. It had the best gig list on the university circuit. And it had a very strong biology and genetics department."

Unfortunately, the first two of these were initially more alluring than the latter. "My first year at university, I didn't do very well either. I got a third and that shocked me again. I really pulled the stops out in the second and third years."

Karen Duff: Neuroscientist and bike enthusiast.

Genetics of disease

The late 1980s were the beginning of a new era in medical genetics, as researchers began to hunt down the genes involved in inherited diseases. For her PhD, Karen went to work in the department led by Bob Williamson, one of the leading figures in the field, at St Mary's in London. By this point, Karen had turned a corner and was devoting all her time to research: "I would work every hour of the day. That was all I wanted to do."

Her PhD, trying to identify genes involved in heart development, proved technically challenging. "I could have spent the first two years on holiday the amount that ended up in my thesis," she says. When her supervisor moved to Cambridge, she found herself working in the lab of the legendary Sydney Brenner. Despite a seven-hour grilling at her viva, she ultimately got her PhD.

She initially planned to continue work on heart development, and made contact with Liz Robertson in the States. As Liz had no position free until the following year, Karen took up a one-year position in London, entering the sphere of Alison Goate and John Hardy, who were on the hunt for genes involved in dementia. When John was lured to the US, a friendship with a researcher in John's lab, Mike Mullan, proved pivotal: "I was drinking buddies with him and he convinced me I should go to Florida."

In the end, a gang of four set up shop in Tampa, Florida. "We used to call it 'Neurodisney'," says Karen. However, the new environment proved a culture shock. Their US hosts were startled by the irreverent Brits, says Karen: "They didn't know what hit them. There was a lot of swearing and that did not go down well at all." Furthermore, the locals' conversations were dominated by boats and beaches:

"THEY DIDN'T KNOW WHAT HIT THEM. THERE WAS A LOT OF SWEARING AND THAT DID NOT GO DOWN WELL AT ALL."

"I just wanted to work in the lab 24/7."

It also proved unexpectedly difficult to recruit people – US researchers preferred the kudos of big-name institutions – and the US grants system initially proved tricky to navigate. Eventually, the funding and papers began to flow: "It was worth the effort. We all got a lot out of that time."

Of mice and money

By this time, Karen had switched to mouse work, developing a mouse model of Alzheimer's disease with mutations in *APP*, the first Alzheimer's disease gene, discovered by John Hardy and colleagues. Mouse models have subsequently formed the core of her research.

Karen rapidly rose through the ranks in Florida, becoming assistant professor, and thrived in her new environment: "America did seem like the land of opportunity," she says. In particular, she leapt on the chance to spend time in other labs, bringing new skills back to Tampa: "I really enjoyed being a roaming scientist."

However, not everything was sweetness and light. The tightness of the community in Florida caused its own stresses and led to some friction – which provided an important scientific life lesson. "Be careful who you fall out with," she advises. People tend to stay in the same field, she points out, so there's a high probability of running into them again: "You can't avoid them, so do not start a vendetta."

A further source of conflict was the desire among some to patent mutations and mouse models. This led to draining and acrimonious disputes about priority and intellectual property rights. "The field came with a lot of high stakes," Karen says. "I've been subpoenaed twice."

After a short stint in Jacksonville, Karen achieved her ambition of moving back to the big city, joining the Nathan Kline Institute just outside New York, following a chance encounter with Sam Gandy in a restaurant in South Korea.

One big advantage was that, as the Institute was state-run, she did not need to apply for animal costs – invariably the biggest chunk of her grant applications: "That opened up my ability to do a lot more mouse research."

At this point she also began to get more interested in tau. "I was firmly on the amyloid side having been associated with John Hardy," she says. However, in the mid-1990s, she began to realise that the tau tangles were a key aspect of Alzheimer's pathology that needed to be modelled. She set herself the demanding challenge of creating a model with the full genomic form of human tau, introns and all. Unfortunately, the mice showed no ill-effects. "So it sat on a shelf for a while. There wasn't much I could do with it."

Her interest in tau put Karen in a small minority of 'tau-ists'. "The tau field was very amusing at that time," she says. "It was only 4–5 people, and half a million amyloid people." This hierarchy was reflected at scientific conferences: "The tau part was always at the end of the big meetings, and always the same people speaking to the same audience." For the mouse modellers, things were even worse: "Being a tau transgenic person, I was always presenting at the end of the end of the end. So everyone had always gone home."

Things changed significantly when, again after a chance meeting, she began a collaboration with Peter Davies at the Albert Einstein College of Medicine in New York. He had a tau knockout mouse strain which he wanted to cross with Karen's transgenic. Lo and behold, the cross developed Alzheimer's pathology.

Gradually, the field woke up to the potential of tau, including Karen: "I had a big love affair with tau, and still do." Of particular note was her landmark work on tau propagation, published in *PLOS One* but garnering hundreds of citations: "It turned out to be massively influential." By restricting human tau expression to the entorhinal cortex, the first brain region involved in Alzheimer's disease, she was able to show that tau pathology appeared to propagate to synaptically connected regions of the mouse brain.

Back home

Karen finished her time in the US at the powerhouse of Columbia University in the heart of New York, one of the world's leading centres for neurodegenerative research. Leaving was a big wrench, she says, but the prospect of heading up the UCL centre was too tempting. She was also concerned about her two daughters, who were attending large metropolitan schools in New York, with gun scanners at every entrance.

As a single parent, it was a difficult time: "Bringing the kids here was a challenge. They were teenagers, they were angry." Things were not helped when, within six months of their arrival, lockdown was imposed.

In fact, this turned out to be a blessing in disguise: "Spending so much time together, the three of us, had a silver lining – how often do you get to spend that much quality time with your teenage kids?"

Workwise, Karen is relishing the opportunity to think more clearly about the research avenues she wants to explore. She has been pleasantly surprised by the breadth and quality of UK and European research, and believes UK researchers should do more to raise their profile among the US research community.

Although the days of sleeping in the lab are now long gone, her enthusiasm for research is undiminished – with collaborators in Japan and a lab at Columbia, days typically start early and end late. It's a far cry from the teenager skipping classes, but that's the effect science can have on people: "I love what I do – it's not a job it's a lifestyle."

Random samples

A quick guide to some of the more unusual brain- and neuroscience-related studies published recently.

Eructation disorder

Socially unacceptable in polite company, belching nevertheless serves a valuable physiological function. For example, Karagama has described 72 patients with a range of debilitating symptoms linked to an inability to burp. They were all successfully treated by application of botulinum toxin (botox) to the cricopharyngeal muscle, a semicircular muscle just below the Adam's apple that controls entry into the eosophagus. Notably, most patients retained the ability to belch beyond 3 months, when the effects of botox are likely to have worn off, suggesting that the condition may reflect a neural dysfunction that interferes with the delivery of signals to the cricopharyngeal sphincter to initiate burping.

Karagama Y. Abelchia: inability to belch/burp-a new disorder? Retrograde cricopharyngeal dysfunction (RCPD). *Eur Arch Otorhinolaryngol*. 2021 Apr 24. doi: 10.1007/s00405-021-06790-w.

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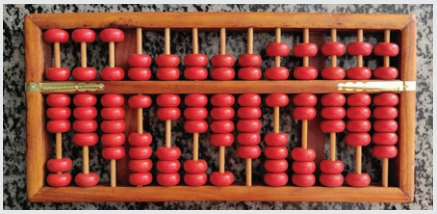

Maths on the brain

Choosing not to study maths A level at school has a significant impact on future earning potential. By focusing on A-level students of similar intellectual abilities, Zacharopoulus *et al*. have shown that decreased GABA concentrations in the middle frontal gyrus could be used to determine whether a student has studied maths. This signature did not reflect pre-existing differences before subject choices were made. It also predicted changes in mathematical reasoning skills more than 1.5 years later. The findings illustrate the reciprocal relationship between education and brain development, and specifically how the lack of mathematical education during adolescence can affect brain plasticity and cognition.

Zacharopoulos G, Sella F, Cohen Kadosh R. The impact of a lack of mathematical education on brain development and future attainment. *Proc Natl Acad Sci USA*. 2021;118(24):e2013155118.

Feats of memory

The study of individuals showing outstanding memory skills could provide insights into the mechanisms of memory. Black *et al*. studied a group of individuals, known as '*Hafiz*' who have memorised the entire Qur'an – 77,449 words in its classic Arabic form. Compared with controls, however, *Hafiz* were no different in their ability to memorise verbal or visuospatial learning. Interestingly, half of the *Hafiz* did not understand Arabic, raising questions about the importance of understanding to long-term memory.

Black R, Mushtaq F, Baddeley A, Kapur N. Does learning the Qur'an improve memory capacity? Practical and theoretical implications. *Memory*. 2020;28(8):1014–1023.

Lizard brains

Lizards are becoming increasingly central to studies of evolutionary neuroscience. To facilitate such studies, Hoops *et al*. have used MRI to generate a 3D segmentation atlas of the brain of the tawny dragon, an Australian lizard widely used in ecological and evolutionary studies. The authors generated a consensus average 3D image from 13 MRI scans, identifying 224 structures across the tawny dragon brain.

Hoops D *et al*. A fully segmented 3D anatomical atlas of a lizard brain. *Brain Struct Funct*. 2021;226(6):1727–1741.

Smarter fasting

Caloric restriction is known to increase lifespan and cognition. Intermittent fasting (such as every-other-day feeding) may have similar benefits while being an easier strategy to adopt. Pereira Dias *et al*. have found that intermittent fasting in mice led to improved long-term memory retention as well as hippocampal neurogenesis. These effects appeared to be linked to enhanced expression of the longevity gene *Klotho* in the hippocampus. The findings suggest that intermittent fasting may be superior to caloric restriction at enhancing cognition, with the effects of intermittent fasting likely mediated through *Klotho*.

Dias GP *et al*. Intermittent fasting enhances long-term memory consolidation, adult hippocampal neurogenesis, and expression of longevity gene *Klotho*. *Mol Psychiatry*. 2021 May 25. doi: 10.1038/s41380-021-01102-4.

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