YOUNG NEUROSCIENCE IRELAND SYMPOSIUM 2018
25TH OCTOBER 2018
Conway Institute
University College Dublin
#YoungNSI18

Keynote Speakers
Prof DAVID NUTT
&
Prof Madeleine Lowery

Conference Booklet


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Jena Bioscience
Dear all,

On behalf of Young Neuroscience Ireland I am pleased to welcome all attendees to University College Dublin for the Young Neuroscience Ireland Symposium 2018.

This symposium gives us the opportunity to bring together early career researchers from across Ireland, including Galway, Cork, and Dublin. The group gathered here today represent the promising future of Irish neuroscience research.

The committee would like to thank all of the invited speakers; David Nutt, Madeleine Lowery, Eilís Dowd, Dervila Glynn, Rachael Clarke, James Linden, Muriel O'Byrne, Ilaina Khairulzaman, Jenny Lennon, and Anita Wdowicz.

We are very grateful for the support and contributions of the following organisations; GreenLight Medicines, Tocris, Medical Supply Company, MyBio, Vector Laboratories, PLOS and The Thesis Centre, Biosciences, and Jena Bioscience.
I would like to thank Derek Costello, Eilís Dowd, Jack Prenderville, and Gary Brennan from the NSI council for their invaluable advice and assistance in organising this meeting.

I am also very grateful to all the committee members who worked very hard to make this event a success; Conor James Mc Veigh, Anne Marie Howe, Audrey Bradford, Brendan O’Donnell, Dwayne Byrne, George Merces, Keira Turner, Lisa Mc Donnell, Phillippa Fowler, Sarah Abdulmalek, Sinead Lanigan, Noelle Enright, Kelvin Lau E-How (FutureNeuro) and AmirAli Farokhniaee.

In conclusion, let me wish you well for your participation in this exciting symposium, and I hope that you will enjoy the scientific and social agenda that we have lined up.

Amy Courtney
Co-Chair of the Young Neuroscience Ireland Symposium Committee 2018
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Programme
Thursday 25th October
Location: Conway Institute, University College Dublin

8.00-9.10 Registration & Coffee

9.10 – 9.20 Welcome Address
Dr. Eilís Dowd, President of Neuroscience Ireland

Session 1: ‘Interdisciplinary Approaches to Problems in Neuroscience’
Chair: George Merces, UCD

9.20-10.10 Keynote Lecture
Professor Madeleine Lowery, University College Dublin
Computational Models of Deep Brain Stimulation for Parkinson’s Disease

10.10-10.40 Keynote Lecture
Dr. Eilís Dowd, NUIIG
Brain Repair for Parkinson’s Disease
10.40-10.55 Dr. Irene Lorente-Folch, RCSI
A combined single-cell imaging and population assay approach to determine and therapeutically target the control principles of neuronal bioenergetics during excitotoxicity

10.55-11.10 Luke Alvey, UCD
In vitro investigation of the effects of topography and mechanical strain on regulation of axon length using 3D printed substrates.

11.10-11.30 Tea/Coffee/Pastries

11.30-11.45 Adriona Kelly, NUIG
A functional analysis of nanotopographical designed platinum iridium electrodes

11.45-12.00 Sarah O'Donovan, UCC
The brain ↔ gut axis in Parkinson’s disease (PD): Alterations in enteric nervous system pathology and gut microbiome in the rAAV-α-synuclein rat model of PD
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<td>Dr. Sarah Roche, UCC</td>
<td>Progesterone: A promising treatment for inherited blinding disease</td>
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<td>12.04-12.07</td>
<td>Dr. Kathy Ruddy, TCD</td>
<td>A different state of mind: Regulating motor cortical excitability using TMS-based neurofeedback</td>
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<td>Electroconvulsive seizure (ECS) in young and middle-aged rats: behavioral, molecular and cellular comparison</td>
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<td>Investigating the relationship between White Matter Microstructure and Neurocognition In Schizophrenia? – An ENIGMA Consortium Study</td>
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<td>Dr. Tom Burke, HSE/UCD</td>
<td>Angiographically Negative Subarachnoid Haemorrhage: A Mixed-Methods Approach and Systematic Review</td>
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<td>Dr. Álvaro Llorente-Berzal, NUIG</td>
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<td>Prospective Pilot Study of neuropsychological functioning in Opioid Dependent Patients</td>
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Session 3: Communications & Outreach Workshop
12.40-13.10 Dr. Dervila Glynn, Cambridge Neuroscience

13.10-14.10 Lunch & Poster Presentations

Session 4: ‘Emerging Therapies in Neuroscience’
Chair: Conor McVeigh, UCD

14.10-14.20 Dr. James Linden, GreenLight Medicines

14.20-15.10 Keynote Lecture
Professor David Nutt, Imperial College London

15.10-15.25 Anne-Marie Howe
Dietary Fats – Inflammatory Impact on the Brain

15.25-15.40 Sravanthi Bandla
Microglia and Myelin are susceptible to BIP inducer X (BIX) induced damage in in-vitro spinal cord explant culture model

15.40-15.55 Rachel Furlong
Mechanisms by which PINK1 regulates PI3-kinase/Akt signalling –exposing novel targets for the treatment of Parkinson’s disease.

15.55-16.10 John-Mark Fitzpatrick
Assessing toll-like receptor signalling as a cannabinoid target in immune cells: Relevance to multiple sclerosis
16.10-16.30 Tea/Coffee/Snacks

**Session 5: Career Paths for Neuroscience PhDs**
Chair: Dr. Rachael Clarke, AstraZeneca

**16.30-17.00** Rachael Clarke – Careers Workshop  
**17.00-18.00** Career Panel Discussion

**18.00-18.10**  
Prize Giving

**18.10-20.00**  
Wine Reception

**20.00**  
Free Shuttle Bus to the City Centre (from Vet Car Park near O’Reilly Hall)

**20.30- late**  
Social Event – Pizza Party @ The Jar, 31 Wexford St, Dublin 2
Invited Speakers
Biographies
Madeleine Lowery is a Professor in the School of Electrical and Electronic Engineering, University College Dublin. Her research is focused on using engineering methods to understand the human nervous system as it relates to movement, in health and disease, and to design therapies and technologies to improve impaired motor function. She leads a research team in the area of Neuromuscular Systems and Neural Engineering. Her research interests include electromyography, bioelectromagnetics, myoelectric control of artificial limbs, electrical stimulation, deep brain stimulation and neural control of movement.

Dr Lowery was a Postdoctoral Fellow then Research Assistant Professor at the Rehabilitation Institute of Chicago and the Department of Physical Medicine and Rehabilitation, Northwestern University. She received B.E. and Ph.D. degrees from University College Dublin. She is a Funded Investigator in the SFI Insight Centre for Data Analytics and the CURAM Centre for Research in Medical Devices. In January 2015 she was awarded a Consolidator grant by the European Research Council.
Dr Eilís Dowd’s research is focused on developing and validating novel pharmacological, cell, gene and biomaterial therapies for Parkinson’s disease. She received her PhD at the University of Edinburgh, UK, after which she completed post-doctoral research at the University of Cambridge, UK, McGill University, Canada and Cardiff University, UK. She then returned to her home country of Ireland in September 2005 to take-up a tenured position as Lecturer in Pharmacology at National University of Ireland, Galway. Dr Dowd is currently President of Neuroscience Ireland, Ireland’s official neuroscience society, and President of the Network for European CNS Transplantation and Restoration (NECTAR), and she sits on the Governing Councils of both the Federation of European Neuroscience Societies (FENS) and the International Brain Research Organisation (IBRO). In her presentation, Dr Dowd will share some of her group’s latest work showing that biomaterials, specifically collagen hydrogels, can dramatically improve the outcome of cellular reparative for Parkinson’s disease, research that was picked-up by the BBC Science Focus Magazine as one of “five incredible advances in brain disease treatment”.
Following on from a degree in Biotechnology, Dervila completed a PhD in Pharmacology (Downing College) and worked for 11 years in the field of Huntington’s disease (HD). Her research focused on understanding the mechanisms underlying neurodegeneration and abnormal behaviour in HD. She left the bench in December 2011 and joined Cambridge Neuroscience. Cambridge Neuroscience is an Interdisciplinary Research Centre within the University of Cambridge connecting >800 researchers across the University, who are involved with research into the nervous system. Her position as Cambridge Neuroscience Strategic Manager involves working with academics from across the University to support the interdisciplinary scientific community in neuroscience. This involves workshops, seminars, facilitating introductions and external interactions, an interactive website, communications and public engagement.
James achieved his PhD in Biochemistry in the Department of Ophthalmology, Queens University Belfast. After a year of researching Alzheimer’s Diseases as a Post-Doc in Neuroscience, Trinity College Dublin), James left the academic world and moved into pharmaceutical sales. After gaining sales experience he then went on to form his own generic drug company in Ireland called Éireceutica Ltd. Here he learned many skills and attributes which he has carried forth into his latest brain-child, GreenLight Medicines. As a scientist and a pharma expert James had the perfect skill set to build GreenLight’s world-beating research network and also to identify which products should be developed and which markets they should be developed for.
David Nutt is currently the Edmund J Safra Professor of Neuropsychopharmacology and Head of the Neuropsychopharmacology Unit in the Centre for Academic Psychiatry in the Division of Brain Sciences, Dept of Medicine, Hammersmith Hospital, Imperial College London. He is also visiting professor at the Open University in the UK and Maastricht University in the Netherlands. He currently is the founder Chair of DrugScience.org.uk. David has edited the Journal of Psychopharmacology for over twenty five years and acts as the psychiatry drugs advisor to the British National Formulary. He has published over 500 original research papers and a similar number of reviews and books chapters. In 2010 The Times Eureka science magazine voted him one of the 100 most important figures in British Science, and the only psychiatrist in the list. In 2013 he was awarded the Nature/Sense about Science John Maddox prize for Standing up for Science and in 2016 an Honorary Doctor of Laws from the University of Bath for contributions to science and policy.
Rachael leads the Education and Engagement team for Sustainability at AstraZeneca empowering 70,000 employees to make decisions aligned with our Values.

This former Neuroscientist, and Compliance Director relishes the opportunity to give Sustainability at AstraZeneca a voice. Specialising in Compliance, Rachael’s passion is to demystify for others. She couples practical knowledge with a Science-led strategy, improving decision making with employee-friendly deliverables, simple in tone and heavy on common sense.

Transforming our Code of Ethics and associated engagement and delivering a community-driven Academy for Sustainability Professionals so they grow with the business, Rachael leads a team that is changing the conversation at AstraZeneca empowering employees to make better decisions and, vitally, showing them they are trusted to do so.
Muriel holds an Honours Bachelor of Science degree from University College Cork and a PhD in Neurochemistry from Trinity College Dublin, 12 months of which was spent at Oxford University as a collaboration with the MRC Anatomical Neuropharmacology Unit. Muriel has nearly 20 years of experience in the pharmaceutical industry gained from R&D roles with major players in the sector. She spent over 10 years based in London with GlaxoSmithKline and AstraZeneca before returning to Ireland to take up a senior level position with Elan. Muriel was one of the first employees in the Dublin office on joining in the summer of 2014. Since then she has contributed significantly to the growth of the office and the expansion of clinical development and regulatory affairs capabilities ex-U.S.
Jenny completed her PhD in Trinity College Dublin in 2014. She then took up the role of Clinical Trials Coordinator in the Children’s Clinical Research Unit (Dept of Respiratory Medicine) Our Lady’s Children’s Hospital, Crumlin. Since June 2016, she has been working as the National Coordinator for CF:INK, the Irish Cystic Fibrosis paediatric clinical trials network. She facilitates and coordinates all clinical trials and research studies run in the six member sites, oversees all aspects of a clinical trial from site selection and set-up, patient recruitment, to study close out. She works closely with a team of Study Coordinators and with the Principal Investigator at each site, to review the study protocols, contracts, budgets and ethics submissions liaises with each Cystic Fibrosis multidisciplinary team, the relevant clinical research organisation, and the study sponsor.
Ilaina joined Sense about Science shortly after completing her research MSc in Immunology from Trinity College Dublin. While doing her MSc, Ilaina was involved in many public engagement activities including teaching teenagers laboratory techniques, competing in FameLab and performing in Bright Club. After a year of bioinformatics research, Ilaina realised she was much more passionate about making societal impact through speaking about science, than she was doing the science. She also has experience in social entrepreneurship, having worked with government bodies and corporations to help them address social challenges in novel ways. Ilaina works on building the VoYS network and encourages early career researchers to start standing up for science.
Anita is a postdoctoral research fellow working under supervision of Prof. Gil Lee in the School of Chemistry Department, UCD. Her current work focuses on use of nanoparticles for separation of Circulating Tumour Cells (CTCs) and characterisation of novel surface chemistries for cell screening. Previously, she completed a postdoctoral fellowship as part of the research group lead by Assoc. Prof. Brian Rodriguez, UCD and gained experience in nano-biotechnology investigating the effects of nano-topographical cues of a ferroelectric material on axonal growth. She graduated with an honours BSc in Genetics and a PhD in Neuroscience, which she completed in the UCD School of Biomolecular and Biomedical Sciences (SBBS) under the supervision of Assoc. Prof Keith Murphy. Her doctoral work focused on the role of immune system modulators in cognition.
History of Irish Neuroscience
Historical Contribution of Irish Neuroscientists and Physicians to Cannabinoid Research and Cannabis as Medicine

Neuroscience Ireland in collaboration with Eilís Dowd¹, Eric J. Downer², David P. Finn¹, Michelle Roche³ and Ethan Russo⁴.

¹Pharmacology, National University of Ireland Galway, Ireland; ²Physiology, Trinity College Dublin, Ireland; ³Physiology, National University of Ireland Galway, Ireland; ⁴International Cannabis and Cannabinoids Institute, Prague, Czech Republic.

Aims: This presentation is designed to highlight how the contributions of 19th century Irish physicians and scientists in the investigation of cannabis therapeutics holds great relevance today as their historical observations have consistently been borne out by modern research.

Methods: The authors’ files were mined for citations on cannabis and their references were systematically investigated for additional data. These were supplemented with history of medicine texts and cross-referenced via PubMed to current investigations on those subject areas.

Results: Medical usage of cannabis spans more than 1000 years, dating to the Anglo-Saxon era. 19th century Irish physicians and scientists were at the forefront of investigation of “Indian hemp” catalyzed by the efforts of William O’Shaughnessy, an Irish physician in India, who examined cannabis in rheumatic diseases, tetanus, cholera and epilepsy in 1838. He examined traditional Indian knowledge and pursued animal experimentation before pursuing human trials, and then sharing his successes with colleagues in Ireland and England. This spurred rapid adoption of cannabis and further experimentation by Michael Donovan for neuropathic pain, Dominic Corrigan for chorea and trigeminal neuralgia, Fleetwood Churchill for uterine hemorrhage, Richard Greene for preventative treatment of migraine, and Edward Birch for opium addiction. When these prior observations are scrutinized in light of contemporary knowledge of the endocannabinoid system, the claims of clinical success are not only confirmed, but perfectly plausible.

Conclusions: Today, this venerable Irish tradition of clinical cannabis research is perpetuated by modern researchers who will continue to benefit by mining the historical evidence.
Ireland’s Historical Contribution to Cannabis Research and Cannabis as Medicine

Neuroscience Ireland with Ethan Russo

19th century Irish physicians and scientists were at the forefront of investigation of the medicinal properties of “Indian hemp”. This was catalyzed by the efforts of William O’Shaughnessy, an Irish physician in India, who examined cannabis in several conditions including epilepsy and delirium tremens. O’Shaughnessy examined traditional Indian knowledge and pursued animal experimentation before pursuing human trials, and then shared his successes with colleagues in Ireland and England.

This spurred rapid adoption of cannabis as a medicine, and further experimentation by Michael Donovan for neuropathic pain, Dominic Corrigan for chorea and trigeminal neuralgia, Richard Greene for preventative treatment of migraine, and Edward Birch for opium addiction.

When these prior observations are scrutinized in light of contemporary knowledge of the endocannabinoid system, these historical claims can be scientifically validated. The venerable tradition of Irish research into the endocannabinoid system and the therapeutic potential of targeting this system continues today.


Sir William O’Shaughnessy
1809-1889

Born in Limerick, Ireland, William O’Shaughnessy obtained his medical degree from the University of Edinburgh in 1829. He took a position as assistant surgeon with the East India Company, and became the first chemistry professor of the Calcutta Medical College. Whilst in India, O’Shaughnessy noted the widespread use of Indian hemp for a “multitude of affections” but he was unable to “trace any notice of the employment of this drug in Europe”. He went on to study and report the efficacy of extracts of Indian hemp for several conditions including epilepsy and delirium tremens.

O’Shaughnessy’s impact on the development of cannabis as medicine was paramount, as his early lectures in England led directly to its widespread adoption there, on the Continent and in North America. In 1843, he became a fellow of the Royal Society, and he was knighted in 1856.

To this day, O’Shaughnessy is often remembered as the father of the modern era of cannabis therapeutics.

Michael Donovan
1791-1876

Michael Donovan was Professor of Chemistry and Pharmacy, and Matron of Medicine of Apothecaries’ Hall, a medical school in Dublin. Donovan was an early adopter of O’Shaughnessy’s new cannabis preparations, and a trailblazer in its application to therapeutic challenges. In 1844 and 1845, Donovan published an impressive series of case studies of patients to whom he provided cannabis after failures of available agents in patients with neuropathic, musculoskeletal and migraine pain.

Richard Greene
1843-1898

Richard Greene was born in Boston to an Anglo-Irish family and graduated from the University of Edinburgh in 1866. He practised medicine in England in the Sussex Lunatic Asylum before becoming superintendent of the Berry Wood Asylum in Northampton. In 1877, Greene published a series of case studies of migraine patients who responded well to cannabis preparations. This work was influential in the subsequent use of cannabis as a prophylactic for migraine headache.

Sir Dominic Corrigan
1802-1880

Dominic Corrigan was born in Dublin in 1802, and obtained his medical degree from the University of Edinburgh in 1825. In 1845, Corrigan published reports of patients with chorea and trigeminal neuralgia responding to Cannabis indica. Corrigan became a Fellow of the Royal Society of Physicians in Ireland in 1856, and their President in 1859. In 1864, Corrigan was knighted and, in 1866, he was made Baronet.

Edward Birch
1840-1912

Edward Birch was born in Dublin in 1840, and obtained his medical degree from the Royal College of Surgeons in Ireland in 1865. He was Principal of the Medical College in Calcutta from where he published his work on the use of cannabis for opium addiction. Birch became a Fellow of the Royal Society of Physicians in London in 1892.
A Virtual Museum of Irish Brain Science

Neuroscience Ireland in collaboration with Richard AP Roche¹, Christina M Ward¹.

¹Department of Psychology, Maynooth University, Maynooth, Co Kildare, Ireland.

**Aims:** Compared to other European countries, Ireland is extremely poor at highlighting and communicating its scientific heritage, in general and in relation to the neurosciences, and Ireland's brain science archives consists of a very modest collection of three major collections (Royal College of Physicians, Royal College of Surgeons, National Archives). This project aims to create a Virtual Museum or digital archive website to collate and present these materials.

**Methods:** By collating relevant materials and documents of interest from the various collections in Ireland, we will establish a website housing a virtual “Museum of Mental Life”, of which brain science and neuroscience will form the backbone.

**Results:** Despite its size, Ireland possesses some noteworthy historical objects – e.g. in the Royal College of Physicians in Ireland (RCPI) archive, and in the Royal College of Surgeons in Ireland (RCSI) collection. There are also further items of interest in anatomy collections and medical departments within the different universities; a survey of these items is ongoing. The website will also contain biographies of key Irish (or Irish-based) figures in the history of brain science, specifically George Berkeley, Gordon Holmes, and George Boole, among others.

**Conclusions:** this project will result in the creation of a virtual Museum of Mental Life, of which brain science/neuroscience will form the core. This website will act as an archival resource housing and/or linking to the contents of the various brain science collections in Ireland, while also flagging the contributions of key figures in the history of Irish brain science.
A Virtual Museum of Irish Brain Science
Christina Ward & Richard A. P. Roche
Maynooth University, Ireland

We are currently developing a website which will serve as a virtual museum of Irish brain science, where we will collate historical items of note from various sources into a cohesive and user-friendly digital archive. Key sources to date include the Royal College of Surgeons, Royal College of Physicians, and the National Library of Ireland. The website will also feature biographical sketches of Irish historical figures who had an impact on the field of neuroscience.

Royal College of Surgeons
The Royal College of Surgeons Ireland (RCSI), houses a 2nd Edition of Andreas Vesalius' text "De Humani Corporis Fabrica", as well as a selection of wax anatomical figures.

- De Humani Corporis Fabrica

A 2nd edition manuscript of this pioneering work from 1555 was written by Andreas Vesalius, the "founder of modern anatomy."

- Wax Anatomical Models

A collection of 22 wax anatomical models are on display in RCSI's Department of Anatomy. 11 of the 22 190-year old models are by the celebrated wax modeller Jacques Tanch, making this the largest collection of Tanch’s work in the world.

Royal College of Physicians
The Royal College of Physicians Ireland (RCPi) houses a broad range of items that relate to neurophysiology, anatomy, pathology and mental health in Ireland.

- Traité D'Anatomie et de Physiologie by Felix Vicq d'Azyr

This neuroanatomy and physiology book dates from 1789. The author, Vicq d'Azyr, was the first to describe the mamillothalamic tract and the substantia nigra.

- Sketch of George Sigerson on his deathbed

A pencil sketch of the Irish neurologist on the day of his death (18 February 1825) by Estella Solomons.

- Pathologiee Cerebri by Thomas Willis

This 1667 text, written by whom many consider "the father of neuroscience", concerns the pathology of the brain.

National Library of Ireland
The National Library of Ireland has a collection of digital and physical resources concerned with aspects of neuroscience such as anatomy, physiology and psychology.

- Cerebri Anatomie by Thomas Willis

This 1667 text contains the first descriptions of the circle of Willis and the first use of the term "neurology", as well as an early characterisation of the cranial nerves.

- Scientific Phrenology: Being a Practical Mental Science and Guide to Human Character by Bernard Hollander

This 1902 text contains over 100 illustrations depicting the skulls of various kinds of people and makes assumptions about their character from measurements of their skull.

- The Relations of Mind and Brain by Henry Calderwood (1879)

Biographies of Prominent Irish Figures
The website will also feature a Biography Section, with short biographical sketches of key figures in the history of Irish brain science written by guest authors who are distinguished in contemporary Irish neuroscience.

- George Berkeley (1685-1753)
- Gordon Morgan Holmes (1876-1965)
- William Thornley Stoker (1845-1912)
- Jonathan Osborne (1794-1864)
- Robert Foster Kennedy (1884-1952)
- Robert Bentley Todd (1889-1986)

And others...

Future Directions
We will continue to search through various archives and collections throughout Ireland to find additional items of historical interest to add to the virtual archive. We will continue to gather material and develop the user interface until the site is ready to publish.

If you would like to be notified when the website goes live or to contribute a biographical sketch to be featured on the website, please email us at: irishbrainmuseum@gmail.com.

A special thank you to FENS for their support in the creation of this project.
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Abstracts
Our eyes are our window to the world. The retina is an integrated outpost of the brain, situated at the back of the eye and housing neuronal photoreceptors that transform incoming light into electrical signals that are sent to and processed in the visual cortex in the brain. Similar to other parts of the nervous system, the retina is susceptible to neurodegenerative disease with devastating consequences. Retinitis pigmentosa (RP) refers to a group of inherited retinal diseases that can cause complete vision loss due to the death of mutated photoreceptors. The most debilitating aspect of this disease is experienced in the later stages, with a loss of colour/daytime vision, hindering a person’s independence to perform everyday tasks such as reading, writing and driving. There is an urgent need to develop treatments for RP that will help to preserve vision and consequently independent living for those affected.

The ultimate goal is to develop a neuroprotective strategy to treat RP, importantly one that will prevent degeneration in the later stages and preserve colour/daytime vision. Our previous work has demonstrated significant neuroprotective properties of Norgestrel, a progesterone analogue, in the mouse retina. The current study further investigates the potential of Norgestrel as a treatment for RP.

We administered a Norgestrel-supplemented diet to a mouse model of RP in the mid-late stages of the disease. We subsequently harvested retinal tissue to assess photoreceptor preservation and synaptic connectivity using immunofluorescence and microscopy. Age-matched mice on a control diet were included for comparison.

Whilst photoreceptor cell death was widespread in the control retina, we observed profound preservation of photoreceptor morphology and synaptic
connectivity in the Norgestrel-treated mice. This was demonstrated by up to 1,600% more photoreceptors following Norgestrel administration.

This work presents Norgestrel as an incredibly promising neuroprotective compound for the treatment of RP. Crucially, Norgestrel could be used in the mid-late stages of the disease to help preserve colour/daytime vision.

Acknowledgements: We thank Fighting Blindness Ireland and Science Foundation Ireland for supporting this work.

A Different State Of Mind: Regulating Motor Cortical Excitability Using TMS-Based Neurofeedback

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To date there exists no reliable method to non-invasively upregulate or downregulate the state of the resting motor system over a large dynamic range.

The aim was to test whether an operant conditioning paradigm which provides neurofeedback of the size of motor evoked potentials (MEPs) in response to transcranial magnetic stimulation (TMS), enables participants to self-modulate their own brain state
Participants were trained to upregulate (increase) and downregulate (decrease) the amplitude of their MEPs, using motor imagery strategies and real-time feedback, over a 5 day period. Simultaneous recordings of brain rhythms using electroencephalography (EEG) were made in order to study the underlying neural mechanisms of this modulation.

Following training, participants were able to robustly increase (by 83.8%) and decrease (by 30.6%) their MEP amplitudes. This volitional up-versus down-regulation of corticomotor excitability caused an increase of late-cortical disinhibition (LCD), a TMS derived read-out of presynaptic GABA\(_B\) disinhibition, which was accompanied by an increase of gamma and a decrease of alpha oscillations in the trained hemisphere.

This approach paves the way for future investigations into how altered brain state influences motor neurophysiology and recovery of function in a neurorehabilitation context.

**Acknowledgements:** Funding from the Swiss National Science Foundation and Irish Research Council

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**Electroconvulsive seizure (ECS) in young and middle-aged rats: behavioral, molecular and cellular comparison.**

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Electroconvulsive seizure treatment is often the treatment of choice for geriatric depression and treatment-resistant depression. Since its discovery in 1938, the mechanisms via which it causes mood elevation has not been clearly understood. Further, considering the physiological differences between young and aged populations, it is extremely important to study the effect of ECS in
older populations. However, most preclinical research has been done on young adults, thus there is a gap in our understanding whether the molecular and cellular effects are similar across age.

The aim of this research was to identify similarities and differences of the effect of electroconvulsive seizure treatment across young and middle-aged rats.

We have systematically compared the effects of chronic ECS administration in young and middle-age male Sprague-Dawley rats, on forced swim behavioural task (FST), hippocampal neurogenesis, detailed hippocampal gene expression profile for trophic factors, developmental signalling mediators, plasticity and extracellular matrix associated genes as well as alterations in recently identified targets of plasticity such as perineuronal nets and reelin.

We found ECS treatment led to antidepressant effects on FST at both ages. We further found interesting overlapping effects in the expression of over 140 genes analysed in the two age groups. Importantly in spite of a ten-fold reduction in hippocampal proliferative capacity with age, we found ECS to enhance proliferation and neurogenesis. In addition, we also found alterations in plasticity markers.

Our results suggest that ECS might cause similar overlapping effect at the two ages. It further adds to our understanding of the consequences of ECS in middle age, and finally suggests plasticity changes to be a probable mechanism to explain retrograde amnesia seen on administering ECS.

Acknowledgements: Minal would like to acknowledge Prof. John Cryan, for allowing her to present her PhD work at this conference and providing funding to attend the conference. All authors thank the support of TIFR-DAE for funding this project and the animal house staff at Tata Institute of Fundamental Research.
Using machine learning analysis to uncover the signature of psychotic experiences in young adolescents: a multi-modal analysis using structural/diffusion MRI, cognition and clinical data

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Psychotic experiences (PEs) are commonly reported in early adolescence and are shown to be a risk factor for psychiatric conditions later in life. Machine learning approaches can be used to discriminate adolescents with PEs from controls using multi-modal data. Understanding the underlying signature of PEs can help uncover biomarkers of the experience and assist in developing early targeted therapies.

The aim of this research is to investigate if adolescents with PEs can be distinguished from controls based on their neuroanatomy, cognitive and clinical profiles.

A machine learning (penalised regression) approach was used to classify PEs versus controls at baseline (11-13 years) with 1) a brain model consisting of structural and diffusion MRI data (n=99) and 2) a brain, cognitive and clinical model (BCC) (n=73). These baseline models were also used to classify PEs longitudinally at follow-up (19-20 years), (brain model (n=51), BCC model (n=32)).

At baseline, the BCC model classified PEs with an AUC of 0.60, while the brain model alone had an AUC of 0.51. Clinical variables and white matter were the top discriminant features in the BCC model. In contrast, the brain model alone had a higher AUC (0.62) compared to the multi-modal model (0.30) when characterising PEs longitudinally. However, the BCC model had very low...
sample size (n=32). White matter in early adolescence was the top most discriminant feature when classifying PEs in later life.

Clinical features such as functioning, bullying, psychopathology and OCD items as well as white matter features appear to be the top discriminant features in the classification of PEs at age 11-13 years. Longitudinally, white matter features at baseline were the top discriminant features in classifying PEs at age 19-20 years.

Acknowledgements: We would like to acknowledge the European Research Council for funding this research


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Cognitive dysfunction is a hallmark characteristic of schizophrenia, a significant predictor of functional outcomes, possibly mediated through neurobiological dysfunction. Neuroimaging studies report grey and white matter volume reductions which are associated with neurocognitive deficits in schizophrenia and healthy controls.

We tested the hypothesis that variation in cognitive performance, as measured by IQ, is partially explained by variation in white matter microstructure. Additionally, we aimed to determine if this effect was larger in patients with schizophrenia than in healthy controls.

Brain diffusion MRI metrics and IQ scores (n=902 patients with schizophrenia and n=1092 healthy controls) were collected from 12 collaborating ENIGMA sites. Data were processed using the ENIGMA DTI-pipeline, and (a) global latent fractional anisotropy component (gFA) and (b) latent fractional anisotropy component for six long association tracts (LA-gFA) were calculated. A site-by-site regression analysis, controlling for age and sex, was carried out to determine the variance in IQ accounted for by gFA or LA-gFA.

gFA accounted for a significant amount of variance in IQ in the full sample (average effect size =0.29), healthy (d=0.25) and patient (d=0.30) samples separately. Similarly, LA-gFA also accounted for significant variation in IQ in the full sample (d=0.30), healthy (d=0.25) and patient (d=0.28) samples separately.
However, the amount of variation in IQ accounted for by either gFA or LA-gFA did not differ between patients and healthy controls.

In the largest study to date, we confirm that variance in global cognitive function is partly accounted for by variation in white matter microstructural organisation. However, these effects are not disorder-specific, suggesting that the deficits in global cognitive function associated with schizophrenia are not explained by white matter alterations, and are instead more likely to be accounted for by other cortical abnormalities.

Acknowledgements: NICOG, NUI Galway and all ENIGMA contributing sites.

The role of childhood trauma severity on working memory BOLD response in patients with schizophrenia

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The role of Childhood Trauma (CT) on working memory brain function in schizophrenia remains poorly understood. Partly, this is due to the variety of CT severity scoring methods used in the literature.

The objective was to examine whether different CT scores are associated with different blood oxygenation level-dependent (BOLD) responses during working memory between patients with chronic schizophrenia (SZ) and healthy controls (HC).
Our preliminary sample consisted of 63 HC and 22 SZ matched for age and sex. All individuals completed the Childhood Trauma Questionnaire (CTQ) and underwent a working memory task in a 3T MRI scanner. Firstly, rescaled ‘Total scores’ were used. Secondly, these individual ‘Total scores’ were categorised into ‘Absent versus present’ levels. Scans were analysed using SPM12 and associations between these two scores with the BOLD response during working memory were assessed using multiple regression analyses.

SZ showed significantly greater CTQ experience than HC. For the ‘Absent versus present’ score, all SZ reported CTQ exposure (0% versus 100%), while approximately 20% of HC disclosed no CTQ history (19% versus 81% of HC).

We observed a significant positive association between the score ‘Absent versus present’ and the right dorsolateral prefrontal cortex and the right angular gyrus \( (P < 0.05; \text{FDR-corrected}) \) in HC only; with similar associations found for the ‘Total score’. In contrast, SZ showed a significant positive relationship between ‘Absent versus present’ scores and the right secondary visual cortex only \( (P < 0.05; \text{FDR-corrected}) \).

These preliminary findings showed that the application of these two scores resulted in group differences, presumably due to the high presence of CTQ scores in SZ which may indicate a potential role of CTQ severity on brain function. Future research will show whether these findings are also found at the brain connectivity level in schizophrenia.

Acknowledgements: This work was funded by grants to GD from the European Research Council (ERC-2015-STG-677467) and Science Foundation Ireland (SFI-16/ERCS/3787).

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**Angiographically Negative Subarachnoid Haemorrhage: A Mixed-Methods Approach and Systematic Review**

Tom Burke\(^1,2,3\), Alan Carr\(^3\), Mohsen Javadpour\(^1,2\), & Niall Pender\(^1,2\).
Clinical outcomes, cognitive assessment, and neuropsychological evaluation in patients with angiographically negative subarachnoid haemorrhage (anSAH) are often interpreted as benign, however, diffuse cognitive deficits have been reported within this cohort. To this end, the present study consists of three distinct yet interlocked projects: 1) A systematic review of cognitive outcomes in anSAH; 2) patients treated in the National Centre for Neurosurgery in Ireland at Beaumont Hospital (n=15) were interviewed about their experience, and the data in relation to cognitive/behavioural/mood changes has been analysed using thematic analysis; 3) the same cohort underwent detailed neuropsychological assessments. Results: Categorically, one participant had no deficits on assessment, and also reported no experience of cognitive difficulties resulting from the anSAH (7%); a further two individuals had no deficits on the battery of cognitive tests, yet self-reported cognitive difficulties (14%); 5 individuals reported no cognitive deficits when the battery would suggest there was impairment (33%); and 7 people reported deficits congruent with the cognitive battery being impaired (46%). Detailed results will be presented as a case series, compared to normative data, contextualised by domain-based impairment with considerations for network-based cognitive impairment. Clinical and theoretical implications will be discussed.

Acknowledgements: We thank the participants for their time in completing this study. Furthermore, we acknowledge the Friends of A in supporting this research.
Acute fear suppresses pain through the phenomenon of fear-conditioned analgesia (FCA), a potent form of endogenous analgesia. The endocannabinoid system within the periaqueductal grey (PAG) mediates FCA. Both the endocannabinoid system and pain processing have been shown to exhibit sexual dimorphism.

To compare the expression of FCA in male versus female rats and investigate associated alterations in elements of the endocannabinoid system in the PAG.

Male and female Sprague-Dawley rats were used. Formalin-evoked nociceptive behaviour was assessed following re-exposure to an arena previously paired with footshock. PAG tissue was subsequently harvested and analysed for levels of anandamide (AEA), 2-arachidonoylglycerol (2-AG) and N-acylethanolamines (oleylethanolamine [OEA] and palmitoylethanolamine [PEA]) by LC-MS/MS, as well as expression of fatty acid amide hydrolase (FAAH), CB1 receptor and peroxisome proliferator-activated receptors (PPARs) α, β/δ and γ by Western blot.

The magnitude and duration of FCA was significantly lower in female rats compared with males. There was no effect of fear conditioning or sex on levels of AEA and 2-AG in the PAG. However, fear-conditioned male, but not female, rats exhibited a significant increase in PAG levels of OEA. A similar pattern was observed in PEA levels. FCA was not associated with any alterations in FAAH or CB1 receptor expression in the PAG of either sex, although females expressed higher levels of CB1 receptor than males. FCA was associated with a significant increase of PPARβ/δ in females, with no changes in males. No FCA-related changes were observed in PPARα or PPARγ, but a sex-dimorphic effect was
observed in PPARγ, with females expressing higher levels of this receptor in the PAG than males.

The magnitude and duration of FCA is lower in female rats compared with male counterparts and sexually dimorphic effects of fear-conditioning on N-acylethanolamine levels and PPAR expression in the PAG are evident.

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Prospective Pilot Study of Neuropsychological Functioning in Opioid Dependent Patients

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Methadone maintenance therapy is the mainstay of treatment for opioid addiction worldwide, particularly in the developed world. It is not without its problems and is a matter of some controversy. There were in excess of 10,000 patients receiving methadone maintenance treatment in Ireland in March 2017, while in the United States The National Survey of Substance Abuse Treatment Services estimated that 306,000 patients were receiving methadone in 2011. A growing body of evidence suggests that patients
receiving methadone maintenance therapy exhibit impairments in cognitive function (Mintzer & Stitzer, 2002). However, it is still not clear what the effects of opioids such as methadone have on cognitive impairment and neuropsychological functioning. These impairments have also been found to be present in former methadone maintained patients following detoxification and prolonged periods of abstinence (Baldacchino et al., 2017; Loeber et al., 2012). No study has attempted to determine when these impairments occur or how degeneration progresses.

The aim of the current study is to compare the neuropsychological functioning of opioid dependent patients across three patient groups (short, medium and long-term users) in an attempt to determine if and at what rate neuropsychological impairments occurs and progresses and whether this differs significantly.

Magnetic resonance imaging (MRI) scanning and neuropsychological instruments will be used. Patients (n=75) will undergo MRI scans and neuropsychological tests. The MRI scans will utilize both structural Diffusion Tensor Imaging (DTI) to examine and quantify the alterations in White Matter (WM) integrity and Functional Magnetic resonance imaging employing a neurocognitive functional (task) imaging technique will be utilized to determine most accurately the period of decline from first episode to long-term (10 years) Methadone maintenance therapy.

This proposed study, which is one of the first of its kind, has the capability to influence in a positive direction, the lives and health status of people experiencing opioid addiction. If the findings are that methadone does not adversely affect neuropsychological and cognitive function, as assessed by structural and functional brain scanning, then confidence will be strengthened in an effective treatment which has been shown to reduce mortality, reduce transmission of blood borne viruses and reduce criminal activity. If on the other hand methadone is shown to adversely affect neuropsychological or cognitive function then informed policy choices can be made to determine the
place of methadone, particularly long term methadone use, in the treatment of opioid addiction.

In Vitro Investigation of the Effects of Topography and Mechanical Strain on Regulation of Axon Length Using 3D Printed Substrates

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Axons in the peripheral nervous system of humans can extend from their cell bodies for over 1.5 metres, but surprisingly little is known of the precise mechanisms that regulate axon length within these nerves.

We set out to develop an in vitro culture system that reciprocated the aligned neurite outgrowth observed in peripheral nerves. Furthermore, we wanted to examine the effects of cyclic uniaxial strain on axon length and path in aligned in vitro cultures.

Dorsal Root Ganglion (DRG) explants were cultured on 3D printed substrates that had aligned parallel micro-ridges on their growth surfaces to facilitate aligned outgrowth of neurites. Elastic silicone substrates were moulded from 3D printed PLA moulds to produce stretchable micro-ridged substrates. A stretching device was designed and built that was used to impose a 5% cyclic uniaxial strain every 24 hours on DRG explants while in culture, and an antagonist of mechanically activated stretch receptors, the tarantula toxin GsMTx-4, was administered to groups of explants to determine the role of stretch receptors in neurite path regulation.

DRG explants projected neurites that aligned with the micro-ridged surfaces of the 3D printed substrates. The mean maximum length of neurites from
cultures on micro-ridged surfaces was over 3 times longer than when explants were cultured on flat surfaces. DRG explants that were subjected to cyclic uniaxial strain on micro-ridged substrates projected longer neurites and had higher axon density than their static controls. Static explants extended their axons mostly in the troughs separating the micro-ridges while the axons of stretched explants were more evenly distributed across the micro-ridges. GsMTx-4 had no effect on axon length but it abrogated an increase of Schwann cell nuclear size observed in stretched explants.

Cyclic uniaxial strain induces increased elongation of axons from DRG explants independent of mechanically gated stretch receptors.

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A Functional Analysis of Nanotopographical Designed Platinum Iridium Electrodes

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The brain machine interface BMI describes a group of technologies capable of communicating with excitable nervous tissue within the central nervous system (CNS). These devices act to directly couple neural tissue with therapeutic stimulating devices or recording systems to control external devices. BMI’s have seen major advances in recent years, but these advances have been impeded due to a deterioration in the signal to noise ratio of
recording electrodes over time following insertion into the CNS. This deterioration has been attributed to an intrinsic host tissue response, namely reactive gliosis, resulting in peri-implant encapsulation via the synthesis of pro-inflammatory signalling molecules and the recruitment of glial cells.

Modification of the nanoscale geometry of the implanted probe could enhance the electrode’s electrical capabilities, and improve the physical coupling between the electrode and the surrounding neurons, whilst reducing gliosis.

In this study, commercially available platinum Iridium (Pt/Ir) microelectrodes and substrates were nanotopographically functionalised via femto/picosecond laser processing to generate Laser Induced Periodic Surface Structures (LIPSS). Four different topographies were analysed for their physical properties using scanning electron microscopy and atomic force microscopy. The electrochemical properties of these interfaces were then investigated using electrochemical impedance spectroscopy. The in vitro response of mixed cortical cultures (embryonic rat E14/E17), was subsequently assessed by confocal microscopy, ELISA and multiplex protein array analysis. Statistical analysis was performed with Mann Whitney.

LIPSS features improved electrochemical properties of the electrodes and promoted cell alignment. Protein array analysis also shows that proteins involved in activation of gliosis were downregulated in LIPSS features compared to control.

Neuroelectrodes functionalised with nanotopographical features could promote chronic neuroelectrode functionality by reducing tissue encapsulation in situ and promoting organised interconnected neural network at the electrode interface.

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A Combined Single-Cell Imaging and Population Assay Approach to Determine and Therapeutically Target the Control Principles of Neuronal Bioenergetics during Excitotoxicity

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Protective effects of ketone bodies and fatty acids in the setting of epilepsy treatment in patients have been described, yet their mechanism of action is not understood. Glutamate is the main excitatory neurotransmitter in the CNS and excessively released during seizures. Over activation of glutamate receptors promotes neuronal dysfunction and death through glutamate excitotoxicity. Interestingly, neuronal excitation and glutamate toxicity can be substantially modulated by alterations in the energy substrates.

The main purpose of this study is to analyse the effects of the metabolic switch imposed by ketogenic substrates on mitochondrial function and neuronal bioenergetics comparing physiological (100 µM) and excitotoxic (1000 µM) glutamate stimulation in ambient and 5 % O₂.

In primary hippocampal and cortical neuron cultures, single-cell imaging using the LSM-5 Live-confocal and LSM-710 Meta-confocal microscopes, High Content Screening analysis using fluorescence and bright field imaging, and bioenergetics assays using the Seahorse-96XF Analyser were conducted.

Neuronal spontaneous activity, analysed by imaging spontaneous cytosolic Ca²⁺ peaks, was observed both in cortical and in hippocampal neurons at 21 % and 5 % O₂ at 9-11 DIV. In basal conditions, fast ATP production was obtained through a prominent increase in glycolysis after glucose injection, associated with oxidative phosphorylation inhibition. However, short chain fatty acids (octanoate) and 3-beta-hydroxybutyrate (ketone body) promoted a moderate to strong increase in mitochondrial respiration, respectively, comparable at 21 % and 5 % O₂. Upon glutamate stimulation, 3-beta-hydroxybutyrate increased glutamate-induced cytosolic Ca²⁺ levels and Ca²⁺-dependent activation of
mitochondrial respiration stronger than substrates glucose or octanoate. At low oxygen, glutamate-induced stimulation of respiration was enhanced and more sustained, and maximal uncoupled respiration was higher.

Using 3-beta-hydroxybutyrate as sole energetic substrate strongly increases calcium signalling and neuronal metabolic capacities, being particularly noticeable in cells growing at low oxygen concentrations.

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The Brain ↔ Gut Axis in Parkinson’s disease (PD): Alterations in Enteric Nervous System Pathology and Gut Microbiome in the rAAV-α-synuclein Rat Model of PD

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Gastrointestinal pathophysiology is a primary symptom of Parkinson’s disease (PD), which precedes motor symptoms by many years. α-synuclein, the major pathogenic species in PD, is present in the enteric nervous system (ENS). It is proposed that α-synuclein may transit from the ENS to brain to initiate PD, and it is known that gut microbiome alterations occur in PD patients. Understanding the two-way communication between the ENS and the central nervous system is thus essential for improving PD diagnostics and
therapeutics. Minimal information is available regarding whether the development of PD in the brain affects the gut.

This study aims to investigate the integrity of the gut ENS and gut microbiome in the adeno-associated-virus-α-synuclein brain-initiated rat model of PD.

Adeno-associated viral (AAV)-driven overexpression of human- α-synuclein (rAAV-α-syn) in the adult rat substantia nigra was employed as a model of PD. The integrity of enteric neuronal and glial systems was investigated in this model, using immunofluorescence analysis of wholemount dissections of the duodenum. Gut microbiota composition was analysed via 16S next generation sequencing and sequenced using Illumina MiSeq, bile acid composition was analysed using UPLC mass spectrometry, key indicators of host health.

Our results show, for the first time, that bilateral intranigral overexpression of α-synuclein significantly alters the gut microbiome at the genus level. Similarly, faecal bile acid levels were significantly increased in the PD model, including a number of primary, secondary, tertiary and free bile acids. Significant correlations were evident between specific bile acids and certain microbiota at genus level. Overexpression of α-synuclein resulted in significant neuronal loss in the ileal submucosal plexus, and a significant increase in glial cell number in the myenteric plexus, indicative of inflammation. Voluntary running protected against both neuronal loss and increases in glial cells, and selectively affected the gut microbiome in the PD model.

Together, these results reveal that developing brain pathology and motor function in this PD preclinical model exerts significant alterations in the gut microbiome and gut ENS, and indicates a brain to gut relationship in PD.

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Dietary Fats – Inflammatory Impact on the Brain

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Obesity is classified as a low-grade inflammatory disorder, associated with an increased susceptibility to Alzheimer’s disease (AD) and aged-related cognitive decline. Toxic amyloid-beta (Aβ) peptides, the primary inflammatory stimuli in AD, result in microglial activation and subsequent neuronal dysfunction associated with this condition. The role of toll-like receptors (TLRs) in mediating this response is well-documented, and we among others have highlighted the prominent role of TLR2 in Aβ-mediated inflammatory changes. Furthermore, peripheral immune cells such as macrophages, can infiltrate the brain under chronic inflammatory conditions ultimately exacerbating the neuroinflammatory environment. Those cells which have been primed by prior exposure to inflammatory-stimuli and diets are likely to have the greatest impact on the brain. We hypothesise that a diet rich in saturated fat (SFA) can promote neuroinflammatory changes and dietary replacement with monounsaturated fats, known to promote metabolic health, could alleviate this negative impact. Furthermore we hypothesise that obese individuals who have encountered repeated TLR2-challenge, such as common respiratory and skin infections, have the greatest risk of cognitive decline.

The aim of this present study is to investigate the inflammatory impact of saturated (SFA) and monounsaturated (MUFA) fats on both macrophage and microglial inflammatory responses and subsequent neuronal impact.

BV2 and N2A cell lines were exposed to dietary fats and TLR2-mediated challenge. Bone marrow derived macrophages (BMDMs) were derived from C57BL/6 mice fed a standard, high-saturated fat (SFA) diet or a high-monounsaturated (MUFA) diet. Markers of inflammation and nitric oxide
release, along with protein expression were assessed using ELISA, Griess assay and western blot.

The priming of BV2 and N2A cells with SFA results in an altered immune response to TLR2-mediated challenge. In addition, an obesogenic diet rich in SFA induces a peripheral immune response in macrophages, a response not seen in MUFA-fed animals.

We conclude that a metabolically healthy obesogenic diet can attenuate specific obesity-induced inflammatory and neuronal changes.

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**Microglia and Myelin are Susceptible to BIP Inducer X (BIX) Induced Damage in In-Vitro Spinal Cord Explant Culture Model**

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BIP inducer X (BIX, 1-(3, 4-dihydroxyphenyl)-2-thiocyanate-ethanone) preferentially induces expression of Binding immunoglobulin Protein (BIP) through the activated transcription factor 6 (ATF6) pathway of the unfolded protein response (UPR) and protects neuroblastoma cell lines and retinal ganglion cells from ER stress induced cell death in vitro. BIX also reduces cell death in pre-clinical cerebral infarct and forebrain ischaemia models indicating it has therapeutic potential.

To determine if BIX enhances myelination in an in-vitro spinal cord explant culture model

Myelinating spinal cord cultures were generated as described in (Thomson et al., 2008). The cultures were treated with BIX or DMSO (vehicle control) from
DIV 18-28 or DIV 28-38 based on the objectives of the experiments. Fixation and staining protocols were performed as described in Linder and Linington, (2014) to quantify: neurite density, myelination, microglia; and cells of the oligodendrocyte lineage. Images were captured with an Olympus BX15 microscope and analysed using Ocular and CellProfiler software, (http://www.cellprofiler.org/). A minimum of thirty images/parameter were analysed from three independent cultures for each biological replicate (n > 3) from at least three biological replicates per condition.

A dose-response study (0.05-10 μg/ml) revealed BIX is selectively toxic with respect to myelination (p<0.0001) amd microglia (p<0.0002). Significant inhibition of myelination and loss of microglia was observed after 5 days (5 μg/ml) in the absence of any significant effect on neurite density or astrocytes. Withdraw experiments demonstrated these effects on myelination and microglia were irreversible. Although BIX inhibited myelination we found it was unable to mediate primary demyelination.

BIX has selective toxicity towards myelin and microglia. Therapeutic use of BIX to protect against ER stress should be considered with caution.

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Assessing Toll-Like Receptor Signalling as a Cannabinoid Target in Immune Cells: Relevance to Multiple Sclerosis

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Toll-like receptors (TLRs) are the sensors of pathogen associated molecules that trigger tailored innate immune intracellular signalling responses. They are expressed on all cells of the immune system and play an important role in immune cell activation and inflammatory responses. Indeed, TLRs have been implicated in many diseases, including neurodegenerative diseases such as multiple sclerosis (MS). MS is a chronic inflammatory autoimmune condition of the central nervous system (CNS) characterised by inflammatory episodes (relapses) that damage the CNS myelin. Cannabinoids are biologically active compounds extracted from the Cannabis plant (phytocannabinoids), synthesised in our bodies (endogenous cannabinoids) or are artificially created (synthetic cannabinoids). Cannabinoids can reduce the symptoms associated with experimental autoimmune encephalomyelitis (EAE) and have therapeutic potential in MS. Indeed, an oral mucosal spray (Sativex®, GW Pharmaceuticals) contains a 1:1 mixture of the phytocannabinoids, tetrahydrocannabinol (THC) and cannabidiol (CBD), and has been shown to palliate symptoms associated with MS. However, the cellular mechanism(s) of action of the components of Sativex are still not fully understood, particularly in immune cells from people with MS (pwMS). A growing body of literature indicates that cannabinoids may cross-talk with TLR signalling events. Indeed, evidence exists which suggests that cannabinoids interact with viral TLR3 signalling through recruitment of interferon regulatory factor 3 (IRF-3), and downstream induction of interferon (IFN)-β\textsuperscript{1,2}. Additionally, the bacterial TLR4 signalling pathway may cross-talk with cannabinoid signalling via inhibition of nuclear factor (NF)-κB signalling and promotion of TLR-domain-containing adaptor-inducing IFN-β (TRIF)-dependent signalling. Data herein illustrate how TLR3 and TLR4 signalling can be modulated by THC, CBD, and a Sativex-like combination (THC:CBD; 1:1; all from GW Research Ltd) in the THP-1-derived macrophage cell line, in terms of IFN-β and CXC motif chemokine-10 (CXCL10) expression. Additionally, some cannabinoids signal through two cannabinoid receptors, CB1 and CB2, however there is increasing evidence that suggests that phytocannabinoids may signal via alternative receptors. Therefore, cannabinoid receptor dependency was determined using CB1 and CB2 receptor antagonists. Finally, the effects of THC, CBD, and a Sativex-like combination of phytocannabinoids
was examined in peripheral blood mononuclear cells (PBMCs) isolated from pwMS, in terms of IFN-β and CXCL10 expression (experiments ongoing).

These findings identify CBD and THC as novel regulators of TLR signalling and highlight TLR3/4 signalling as a mechanism to be investigated in the development of new cannabinoid therapeutics for the treatment of disorders such as MS.

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**Mechanisms by Which PINK1 Regulates PI3-Kinase/Akt Signalling – Exposing Novel Targets for the Treatment of Parkinson’s Disease**

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PI3-kinase/Akt signalling is central to cell survival, metabolism, protein and lipid homeostasis, and is impaired in Parkinson's disease (PD). Akt activation is reduced in the PD brain, and by many PD-causing genes, including PINK1. However, mechanisms underlying PINK1’s function in PI3-kinase/Akt signalling remain unclear.
This study aimed to delineate the mechanisms by which PINK1 regulates Akt signalling, in order to determine the role of PINK1 in the altered Akt signalling that occurs in PD.

Immortalised mouse embryonic fibroblast lines (MEFs) derived from PINK1+/+ or PINK1−/− mice, and PINK1−/− MEFs expressing human PINK1 or triple kinase dead PINK1, were employed and analysed by western immunoblotting, immunofluorescence, and mass spectrometry.

Our results reveal for the first time that PINK1 constitutively activates Akt in a PINK1-kinase dependent manner, in the absence of growth factors. We also show that PINK1 enhances Akt activation in normal growth medium, by increasing Akt phosphorylation at Ser473 and Thr308 residues. Rapid and transient agonist-induced production of PI(3,4,5)P3 at the plasma membrane is essential for initiation of Akt signalling, recruiting inactive cytosolic Akt to the plasma membrane. We present new evidence that PINK1 kinase activity significantly accelerates the localisation of GFP-Akt-PH and PI(3,4,5)P3 to the plasma membrane in immediate response to IGF-1. In addition, we show that His- tagged PINK1 colocalises with PI(3,4,5)P3 in normal growth medium. Increasing evidence shows that PI(3,4,5)P3 is important for long-term agonist-induced activation of Akt within endomembrane compartments. In line with this, we demonstrate that PINK1 significantly enhances a time- and PINK1 kinase activity-dependent increase in localisation of PI(3,4,5)P3 to the Golgi in response to sustained IGF-1 stimulation.

This study demonstrates a new role for PINK1 as a primary upstream activator of Akt via PINK1 kinase-dependent regulation of its primary activator PI(3,4,5)P3, providing novel mechanistic information on how loss of PINK1 impairs Akt signalling in PD.
Brain predicted age difference as a cognitive ageing biomarker

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Brain-predicted age difference (brainPAD) is a potential biomarker of unhealthy ageing. BrainPAD can be calculated by subtracting an individual’s chronological age from their ‘brain’ age, as predicted from machine learning analysis of neuroimaging data. A positive brainPAD score indicates an ‘older’ appearing brain and is associated with increased mortality risk and poorer physical and cognitive ageing. However, the relationship between brainPAD and cognitive ageing has not yet been fully explored, particularly within non-clinical populations. The relationship between brainPAD and specific measures of cognitive function in healthy older adults will be investigated. 1,359 T1-weighted MRI scans were downloaded from open-access repositories and preprocessed. Voxelwise grey matter density values were extracted and used as the training set in an Elastic Net machine learning model with 10-fold cross validation. The coefficients from this machine learning model were then applied to MRI data from two independent datasets, the Irish Longitudinal Study on Ageing (TILDA) and a dataset from Dokuz Eylul University in Turkey in order to generate brainPAD scores for these cohorts. In the training set, the Elastic Net model significantly predicted age from T1 MRIs (r = 0.89, p < 0.0001). Applying these coefficients to the TILDA dataset also generates significant predictions of age within this cohort (r = 0.63, p < 0.0001). These coefficients will also be applied to the Dokuz Eylul University dataset to establish the generalisability and replicability of this model. Subsequently, the relationship between brainPAD scores and specific measures of cognitive function (information processing speed, memory, executive function, and
sustained attention) will be investigated in both datasets. These results support the use of Elastic Net for predicting brain age. Evidence of a relationship between brainPAD scores and cognitive function might provide support for the use of brainPAD as a cognitive ageing biomarker.
Genes influenced by MEF2C contribute to variance in cognitive ability in the general population

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Myocyte enhancer factor 2 C (MEF2C) is a transcription factor that plays a central role regulating cell differentiation, proliferation, survival and apoptosis. MEF2C has been implicated in each of the most recent GWAS of cognitive ability (CA) and educational attainment (EA). Animal studies have indicated that knockout of Mef2c interferes with healthy development of brain regions associated with cognitive function, e.g. hippocampal dentate gyrus, neocortex. Furthermore, mutation/deletion of MEF2C can cause severe intellectual and developmental disability. We therefore hypothesised that genes regulated by MEF2C would be associated with cognitive function. In order to test this we constructed a list of genes whose expression is influenced by MEF2C. We then tested this list for association with genes known to be associated with CA and EA. We created a set of differentially expressed genes (DEGs) based on an RNA-seq study that captured the transcriptional changes in mouse adult brain that result from early embryonic deletion of Mef2c in cortical and hippocampal excitatory neurons. This mouse DEG list was converted to human orthologues (n=1052) and tested for enrichment of genes associated with 1) CA, and 2) EA, using MAGMA and recent GWAS summary statistics for each phenotype. We also performed hypergeometric tests to investigate if the DEGs were enriched for current primary intellectual disability (ID), autism, and loss-of-function (LoF) intolerant (i.e. highly constrained) genes. We then used Ingenuity Pathway Analysis (IPA) to explore functional pathways implicated by the MEF2C DEGs. The DEGs were significantly enriched for CA (p<0.001) and EA (p<0.001) genes; along with ID (p<0.01), autism (p<0.01) and LoF intolerant (p<0.001) genes. The top functions IPA predicted to be decreased from these DEGs are 'development of neurons' (p<0.001, z-score=-2.0) and 'formation of cellular protrusions' (p<0.001, z-score=-2.1). These findings indicate that genes influenced by MEF2C are highly constrained
and contribute to cognitive function and neurodevelopmental disorders with severe cognitive deficits.

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The effect of DOPAL on the bioenergetic performances of primary olfactory bulb mixed cultures

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The olfactory bulb (OB) is one of the first places affected by neurodegenerative disorders, including Alzheimer’s and Parkinson’s disease (PD). In PD, a reduced ability to detect odours (called hyposmia), is one of the prodromal symptoms, affecting patience up to decades before the diagnosis of the disease is made. Increased concentration of DOPAL, a metabolite of dopamine, have been associated with PD progression. The presence of dopaminergic neurons and thus DOPAL in the OB could explain the high vulnerability of this region. The aim of this work is to explore the effect of DOPAL on the energy machinery of the cells using two approaches: an acute injection of DOPAL or a pre-treatment of DOPAL to mimic a chronic exposure. Primary OB mixed cells have been obtained from postnatal rats. Cells were cultured for at least 7 days before any experiment was performed using the Seahorse extracellular flux analyser and the Mito Stress test assay. DOPAL treated cells display signs of mitochondrial dysfunction. While ATP synthesis is not affected, an increased proton leak, a measure of a damaged mitochondrial membrane, has been detected with increasing doses of DOPAL. Also the coupling efficacy of treated cells is significantly lower compared to controls. Non-mitochondrial oxygen consumption decreases after acute exposure to DOPAL but is not affected in the pre-treated group. The bioenergetic healthy index is significantly lower in the DOPAL groups. DOPAL has a deleterious effect on the mitochondria, impairing the physiological energy production. Different response has been detected between pre-treated and acute cells, highlighting different mechanism of action between an acute versus a more chronic model.

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Development and characterisation of a photocrosslinkable hyaluronic acid hydrogel used to 3D print nerve guidance conduits to promote nerve regeneration

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Regeneration of the spinal cord after injury remains a great challenge due to the complexity of this organ. Inflammation and gliosis at the injury site hinder the outgrowth of axons and hence prevent synaptic reconnection and reinnervation. Implantable biomimetic biomaterials have proven to be an exciting tissue engineering approach to promote axon outgrowth across the injury site. Hydrogels provide a substrate for cell adhesion and migration while also reducing inflammation after injury. Hyaluronic acid (HA) is the main component of the spinal cord extracellular matrix and plays a vital role in cell proliferation and axonal guidance. In this study, we have characterised a photo-crosslinkable HA-tyramine hydrogel from a chemical, mechanical, electrical, and biological perspective. The aim would be to develop photocrosslinkable biomimetic hydrogels for neural tissue engineering applications. Using rheology, the mechanical properties of HA-tyr in response to incremental increases in UV exposure was measured and compared to that of isolated rodent spinal cord tissue. Using potentiometry, the electrical conductivity of HA-tyr was examined. Using the Nanoscribe two-photon polymerisation (2-PP) 3D printer, HA-tyr was photocrosslinked according to computer aided Design (CAD) created geometries. The cytocompatibility of photocrosslinking HA-tyr was assessed using dorsal root ganglion explants and immunohistological staining. From our experimentation, we have examined the degree of tyramine functionalisation of HA via nuclear magnetic resonance spectroscopy. We have found that the mechanical properties of HA-tyr can be tuned to mimic that of native spinal cord via optimization of the photo-initiator concentration and UV exposure. Using potentiometry, the electrical conductivity of photocrosslinked HA-tyr was assessed and compared to that of native spinal cord tissue at physiologically relevant depolarisation frequencies. Using dorsal root ganglion explants, the cytocompatibility of photo crosslinked HA-tyr was assessed using immunohistochemistry. Finally, using 2-PP, 3D printing of HA-tyr was optimised in term of laser power and printer scan speed.
In this study, we have developed a biocompatible, biomimetic hydrogel that can be used for photolithographic 3D printing to fabricate tissue engineered constructs for neural tissue engineering applications.

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The human dorsal hippocampal commissure: Using high resolution tractography to delineate the afferents traversing this midline structure

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Considered the primary pathway of communication between the right and left hippocampal and parahippocampal limbic systems, the dorsal hippocampal commissure (DHC) crosses the midline on the lyra of the fornix. Although much research has been conducted into this structure in animal studies, there is a paucity of research in humans, particularly concerning the regions to which it connects. Though considered the primary hippocampal commissure, animal studies have shown that the majority of fibres are parahippocampal in origin. The purpose of this investigation was to determine which key limbic regions are connected by this commissure. The data has been correlated with age and gender. Another aim was to determine whether differences exist between this structure in the depressed cohort compared to healthy controls. High-resolution T1, T2 and high angular resolution diffusion imaging (HARDI) was used to scan 43 healthy controls and 31 depressed subjects at Trinity College Institute of Neuroscience. Constrained Spherical Deconvolution (CSD) was used to calculate tracts. After isolating the DHC using an anatomically derived protocol, segmented volumes (the parahippocampal gyrus, hippocampus, temporal pole and amygdala) were used to calculate the proportion of fibres originating from each region. Ethics was granted under the remit of the REDEEM study. In keeping with animal studies, the parahippocampal region is the primary site of origin of the DHC. There are significant reductions in volume and FA with age but no significant differences between the depressed and the healthy cohort. Our findings suggest that the parahippocampal gyrus may exert more influence on the human contralateral limbic system than previously thought, with consequences in how we conceive of limbic circuitry. Though there is no effect in depression, our technique and results may have implications for memory, clinical (Alzheimer's and other neurodegenerative diseases) and epilepsy research, as well as putative treatment.
Exosomes are biological nanoparticles produced by most cell types that mediate intercellular transfer of some proteins, mRNAs and miRNAs, including the pro-inflammatory miRNA miR-155. miR-155 containing exosomes are released from peripheral macrophage cells and can transfer the miRNA to other cells in inflammatory conditions with functional consequences. In multiple sclerosis an increase in quantity in the CSF and serum is observed, and recently exosome-associated miRNAs have been suggested as potential biomarkers for different types of the disorder. The aim would be to establish in vitro and ex vivo tools that may be used to assess the role of exosome-mediated intercellular transfer of miR-155 from macrophages to CNS cells in the context of neuroinflammation, particularly multiple sclerosis. Mixed glia cultures and myelinating organotypic brain slice cultures were prepared from C57Bl/6 neonates (p3-5 and p1-2, respectively) and stained for markers to distinguish astrocytes, microglia and oligodendrocytes in the former model, and axons and myelination in the latter. In vitro mixed glia cultures positive for differentiating oligodendrocytes, astrocytes and microglia were successfully established, as were ex vivo myelinating organotypic brain slice cultures of the cerebellum and brain stem, as demonstrated by the displayed images. The cultures established above provide in vitro and ex vivo tools to investigate exosome-mediated transfer of miR-155 from peripheral macrophages to CNS cell populations, and initial exploration of functional consequences in MS-related processes.

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The effect of inflammatory microglial factors on astrocytes in a human induced pluripotent stem cell-derived in vitro model of neurodegeneration

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Emerging evidence supports a neuro-injurious role of astrocytes in neurodegeneration, with astrocytes developing a reactive phenotype when exposed to inflammatory microglial factors (Liddelow et al. 2017). Following this, we aimed to examine this classification in human cells. Human induced pluripotent stem cells (iPSC) may be derived from human somatic cells and subsequently patterned into numerous cell types. The ability to derive astrocytes and neurons from iPSC provides a powerful in vitro model of CNS disorders. The aim of this study was to first characterise iPSC-derived astrocytes and to subsequently induce a reactive astrocyte in order to generate a reactivity profile, and investigate the effect of reactive astrocytes on iPSC-derived neurons. Human iPSC were patterned towards a neural fate using dual SMAD inhibition (Chambers et al. 2009) to produce neural progenitor cells (NPC). Subsequently, astrocytes were derived using epidermal growth and human leukemia inhibitory factors (Serio et al. 2013) to produce mature astrocytes after 90 days. Astrocytes were characterised by immunostaining for GFAP, S100β, Connexin-43 and EAAT1, then stimulated (IL-1α, TNFα and C1q) to induce reactivity and a reactivity profile was generated via ELISA and qPCR analysis. NPC were matured and treated with astrocyte conditioned media (ACM), stained for β-tubulin and quantified by cell counting. iPSC-derived astrocytes are positive for astrocyte markers GFAP, S100β, Connexin-43 and EAAT1 confirming cell fate. Stimulation with microglial factors resulted in increased IL-6, RANTES and GM-CSF secretion. qPCR analysis showed increased expression of genes associated with reactivity including IL-6, ICAM1, LCN2 and SERPINA3. ACM from reactive astrocytes diminishes neuronal health indicated by increased γH2AX+ neurons and a significantly decreased number of neuronal clusters in culture. The ability to produce reactive astrocytes in vitro in human cell lines provides a powerful model for researching the mechanisms underlying the detrimental role of astrocytes in neurodegeneration.
The relationship between levels of alcohol use and self-advantageous social decision making within a student population

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Previous research has found that people with alcohol dependence are more likely to reject unfair offers than healthy controls in economic games that assess self-advantageous social decision making. The aim of the present study was to investigate whether levels of alcohol use affected self-advantageous social decision making in a university population during trials of the Ultimatum Game (UG). Sixty-nine university student participants (32 male, 36 female, 1 other) completed an online survey via Qualtrics. First, they completed the Alcohol Use Disorder Identification Test (AUDIT) questionnaire which established their regular levels of alcohol use, followed by completing the UG. It was hypothesised that people who drink no alcohol would accept more offers with a relation between higher levels of alcohol consumption and offer acceptance. The results found that increased alcohol consumption was not predictive of self-advantageous social decision making behaviours as depicted by performance on the UG. Findings indicate that the amount of regular alcohol use a population of university students consume does not predict outcomes in this domain of social decision making. However, interventions should be implemented at this early stage in order to combat the deleterious effects long-term alcohol abuse can have.

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Assessment of neurotrophin-functionalised biomaterial hydrogels using ventral mesencephalic tissue explants in context of Parkinson’s disease therapeutics

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Biomaterial-based therapies offer significant potential in regenerative approaches for Parkinson’s disease (PD). For preliminary *ex vivo* assessment of the efficacy/safety of such approaches, the use of explanted tissue containing the dopaminergic pathways affected by PD provides significant advantages over the use of cell culture models. Thus, the aim of this study was to assess the utility of ventral mesencephalic tissue explants for assessment of the efficacy and safety of GDNF or GDF-5 functionalised collagen hydrogels *ex vivo*. For this study, 30 embryonic day 14 rat embryos were dissected to obtain the mesencephalic-diencephalic tube which was maintained in tissue culture using the air media interface method$^2$. Explants were then exposed to 5 µg/µl GDF-5 or GDNF either as a bolus or encapsulated in a collagen hydrogel for various time-points, after which they were fixed for histological analyses. Free floating tyrosine hydroxylase immunohistochemistry was completed to identify survival and development of dopaminergic neurons. Exposure to the collagen hydrogels did not have any detrimental effects on the explanted tissue viability *ex vivo*. Moreover, when the hydrogels were functionalised with GDNF or GDF-5, this improved dopaminergic axonal outgrowth from the cells. This experiment successfully demonstrates the utility of ventral mesencephalic tissue explants for assessment of the efficacy/safety neurotrophin-functionalised collagen hydrogels. This approach offers advantages over cellular models for the preliminary assessment of biomaterial-based regenerative therapies for PD.

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Duchenne Muscular Dystrophy (DMD), a heritable X-linked recessive disorder which affects approximately 1 in 3500 live male births, occurs due to loss of the cytoskeletal protein, dystrophin. Dystrophin has a crucial role in protecting skeletal muscle from contraction-induced damage but is also expressed in neurons of some brain regions, such as the hippocampus. An absence of dystrophin can result in dysfunctional synapses in both DMD boys and the dystrophin-deficient \( mdx \) mouse, and DMD patients exhibit significant deficits in cognitive function (1). Chronic inflammation in DMD is associated with elevated circulating levels of the pro-inflammatory cytokine, interleukin-6. Although typically found at low levels in the healthy brain, IL-6 can be elevated in diseased brains where cognitive function is also impaired (2, 3). The aim of this study was therefore to determine if IL-6 receptors (IL-6Rs) are co-expressed with dystrophin at hippocampal synapses. If so, this may indicate a role for IL-6 in dysregulated synaptic transmission associated with loss of dystrophin. Dissociated hippocampal neurons (3-5 day old) from dystrophin-expressing C57BL/6 mice were cultured for 10-12 days in culture medium with or without supplemental recombinant IL-6 (1nM). Immunofluorescence and confocal microscopy were used to visualise fixed hippocampal neurons labelled with antibodies against IL-6 receptors, synaptophysin and dystrophin (n=3 cultures). RT- qPCR was used to compare gene expression of IL-6 and IL-6R in WT and \( mdx \) hippocampal tissue (n=10 per group). IL-6R expression was present in cell bodies and processes of cultured hippocampal neurons and was co-localised with the pre-synaptic marker, synaptophysin. Incubation with supplemental IL-6 resulted in clustering of IL-6Rs, particularly within neuronal somata. Dystrophin expression was also evident in synaptophysin-expressing clusters but was unaffected by incubation with IL-6. Although peripheral IL-6 is elevated in both DMD patients and \( mdx \) mice, we did not find any differences in the gene expression of IL-6 (p>0.05) or IL-6R (p>0.05) between our WT or \( mdx \) hippocampal tissue. These findings indicate that pre-synaptic IL-6Rs may
interact with dystrophin and contribute to synaptic transmission in hippocampal neurons. Although we did not detect differences in overall hippocampal of IL-6Rs in WT and \textit{mdx} tissue using RT-qPCR, further studies examining synaptic expression of IL-6Rs in dystrophin-deficient \textit{mdx} mouse hippocampal neurons may help to elucidate the possible role of this cytokine in dystrophin-deficient associated cognitive dysfunction.

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Autism is a neurodevelopmental disorder characterised by impaired social and communication skills. In addition to these classical behavioural symptoms, increasing evidence indicates that individuals with autism exhibit altered pain perception and expression. However, it is unknown if sexual dimorphism exists in the processing and expression of pain in autism. Clinically relevant animal models provide a means to study the expression and physiological mechanisms underlying altered pain processing in autism. To evaluate if sexual dimorphism exists in nociceptive responding in the valproic acid (VPA) rat model of autism. Pregnant female Sprague Dawley rats received VPA (500mg/kg; s.c.) or saline at GD12.5. Male and female offspring (PND43-49) underwent nociceptive testing in the hot plate test (thermal nociception), the von Frey test (mechanical nociception), acetone drop test (sensitivity to cold innocuous stimulus) and formalin test (inflammatory pain). Male and female VPA-exposed rats exhibited increased latencies to respond in the hot plate test when compared to saline treated counterparts. Male and female VPA-exposed rats exhibited increased withdrawal thresholds in the von Frey test when compared to saline treated counterparts. There was no difference between VPA and saline-treated rats in the acetone drop or formalin test. Adolescent male and female rats prenatally exposed to VPA display higher thresholds for both thermal and mechanical nociceptive stimuli, indicating thermal and mechanical hypoalgesia. These data mirror clinical findings in individuals with autism and thus the VPA model may provide an important means of evaluating changes in nociceptive processing associated with autism.

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Modulating the brain’s beta rhythm using brain-computer interface to enhance inhibitory control

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The ability to inhibit unwanted behaviours is reliant upon effective inhibitory control (IC) in the brain. Poor IC is characteristic of a wide range of psychiatric conditions. The Stop Signal Task (SST) is a lab-based measure that is sensitive to this deficiency, quantifying the time taken to cancel a response that has already been initiated. A strong increase in the amplitude of rhythmic brain oscillations in the beta (15-30 Hz) frequency band are registered in electroencephalography (EEG) recordings accompanying ‘stopping’. As newly emerging theories propose that brain rhythms are causal to behaviour, rather than simply epiphenomenal, we investigated whether the ability to flexibly modulate the beta rhythm underlies IC. Participants (n=24) were divided into four groups, who undertook EEG neurofeedback training. Six were trained to upregulate, and six to downregulate the right frontal beta rhythm. A control group were trained to upregulate (n=6) or downregulate (n=6) the alpha rhythm. Training occurred over six days. Behavioural performance on the SST was measured pre and post training. Preliminary results indicate that participants are capable of learning to modulate the right frontal beta and alpha rhythms. During performance of the SST a strong increase in right frontal beta at a time point corresponding to stop signal reaction time (SSRT) was detected, and used for localisation of the signal driving the neurofeedback display. To date we have demonstrated that the protocol is feasible and shows promising results for neuromodulation. Whether beta training impacts upon SSRT remains to be seen (results pending).

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The effects of optogenetic modulation of rat anterior cingulate cortical glutamatergic neurons on the affective component of pain

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The anterior cingulate cortex (ACC) plays an important role in top-down control and the affective component of pain. \textit{In-vivo} optogenetics is a technique in which light-sensitive proteins, opsins, are used to modulate target populations of neurons with high temporal control in awake behaving animals. Commonly used opsins are channelrhodopsin-2 (ChR2) and archaerhodopsin (Arch) to activate or silence neurons, respectively. Optogenetic methodology has been a valuable tool in a wide range of neuroscience fields including pain research. The aim of this study was to investigate the effects of optogenetic modulation of glutamatergic neurons in the ACC on formalin-evoked aversion and nociceptive behaviours in rats. Adult male Sprague-Dawley rats (n=10 per group) underwent stereotaxic injection of adeno-associated virus (AAV) and implantation of optic fibres into the ACC. The AAV encoded control fluorophores, ChR2, or Arch under regulation of calmodulin kinase II alpha (CamKII\textalpha) promoter for selective expression within glutamatergic neurons. Four weeks later, the effects of optogenetic stimulation on formalin-induced conditioned place aversion (F-CPA) were assessed. Data were analysed using one-way ANOVA. We found that optogenetic inhibition of glutamatergic neurons in the ACC abolished F-CPA, while activation of the same neurons did not significantly affect F-CPA, compared with rats expressing the control fluorophore. These data suggest that glutamatergic neurons of the ACC play an important role in the aversive component of inflammatory pain in rats.

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Kappa opioid receptor-mediated modulation of social motivation and cognition in adolescent rats

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Negative affect and deficits in social behaviour are a hallmark of several psychiatric and neurodevelopmental disorders. The opioid system is widely recognised to regulate social behaviour, with mu-opioid receptor agonism increasing, and kappa-opioid receptor (KOP) agonism decreasing, social play behaviour\cite{1}. However, there is a paucity of data examining the effects of modulating KOP activity on other aspects of social responding. To investigate the effects of KOP modulation on social motivation and cognition in adolescent rats. Adolescent male Sprague Dawley rats received single, acute administration of the KOP agonist U50488 (2.5mg/kg, s.c.), KOP antagonist DIPPA (5mg/kg, s.c.), or vehicle. Social motivation and cognition were assessed using the 3-chamber sociability test. Data revealed that all rats showed a preference for a social (rat) over a non-social (empty cage) stimulus. KOP antagonism (DIPPA) significantly increased the time interacting with a social stimulus, compared to vehicle-treated counterparts. There was no effect of KOP agonism on sociability. Assessment of social novelty preference revealed that vehicle-treated animals exhibited a preference for the novel over the familiar rat, an effect not observed following KOP agonism or antagonism. Analysis of distance moved in the arena revealed that neither U50488 nor DIPPA altered locomotor activity. These data demonstrate that KOP agonism reduces social novelty preference while KOP antagonism enhances sociability and reduces social novelty preference. Thus, the KOP is a key regulator of social motivation and cognition, and may represent a therapeutic target for the treatment of disorders associated with impaired social responding.

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Social behavioural deficits in the valproic acid animal model of autism revealed following administration of the viral mimetic PolyI:C to female rats

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Stroke is the leading cause of disability in the Western world and the third most common cause of death. Acute ischemic stroke (AIS) represents approximately the 85% of all strokes and is caused by clots that obstruct blood vessels supplying the brain. The characterization of blood clots obtained by thrombectomy from patients affected by AIS is an emerging area of research. Often, as clot fragments are being removed, some of the clot is removed relatively easily, but the remainder may take multiple passes. We aim to study the heterogeneity within clots in order to gain an understanding of the composition of the most difficult ones. To date, more than 200 cases have been collected from two European partner hospitals in Dublin and Gothenburg. Histological analysis using Haematoxylin & Eosin (H&E) and Martius Scarlet Blue (MSB) stain has been performed using Orbit Image Analysis. Within the initial 50 cases analysed using the specimens received from two partner hospitals, 11 cases (22%) required multiple passes to successfully remove the clot. Our initial results have shown that clot fragments that are difficult to remove have increased platelet and fibrin composition, together with a reduction in red blood cells percentage. According to the preliminary data, a trend in within-clot heterogeneity has been observed in the cases that require multiple passes for their successful removal. Their characterization will be helpful to advance therapeutic approach, especially for the most difficult cases.

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Individual differences in learning from probabilistic reward and punishment predicts smoking status

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The ability to update reward and punishment contingencies is a fundamental aspect of effective decision-making, requiring the ability to successfully adapt to the changing demands of one’s environment. In the case of nicotine addiction, research has predominantly focused on reward- and punishment-based learning processes among current smokers relative to non-smokers, whereas less is known about these processes in former smokers. The aim of the current study was to examine differences in learning from positive versus negative feedback in current, ex-, and non-smokers. In a total sample of 105 students, we used the Probabilistic Selection Task to examine differences in reinforcement learning among 41 current smokers, 29 ex-smokers, and 35 non-smokers. The PST was comprised of a training and test phase that allowed for the comparison of learning from positive versus negative feedback. The test phase of the Probabilistic Selection Task significantly predicted smoking status. Current and non-smokers were classified with moderate accuracy, whereas ex-smokers were typically misclassified as smokers. Lower rates of learning from rewards were associated with an increased likelihood of being a smoker or an ex-smoker compared with being a non-smoker. Higher rates of learning from punishment were associated with an increased likelihood of being a smoker relative to non-smoker. However, learning from punishment did not predict ex-smoker status. Current smokers and ex-smokers were less likely to learn from rewards, supporting the hypothesis that deficient reward processing is a feature of chronic addiction. In addition, current smokers were more sensitive to punishment than ex-smokers, contradicting some recent findings.
Injectable collagen hydrogel for intra-striatal delivery of anti-inflammatory cytokines in Parkinson’s disease.

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The site specific delivery of anti-inflammatory factors using injectable biomaterial scaffolds has the potential to target the elevated inflammatory response present after cell transplantation therapy in Parkinson’s disease and therefore increase graft survival. The aims of this study were 1) to assess the biocompatibility of type 1 bovine collagen hydrogels of various cross-linker concentrations in vitro and in vivo, and 2) to assess the ability of the hydrogels to retain IL-10 in the striatum in vivo. In vitro, primary neural cultures were incubated with preformed collagen hydrogels for 24 h, and biocompatibility was assessed using cell viability assays and immunocytochemistry. In vivo, 24 male Sprague Dawley rats were given a bilateral intra-striatal delivery of 1000 ng of IL-10 as a bolus or encapsulated in collagen hydrogels. Polymerisation, biocompatibility, biodegradability and IL-10 retention were assessed at days 1, 2 and 4 using immunohistochemistry. Collagen hydrogels were cytocompatible with primary neurons in vitro, successfully polymerised in situ in the brain, where they were also biocompatible and biodegradable. Most importantly, injection of IL-10 within the collagen hydrogel resulted in significant retention of the anti-inflammatory cytokine in the striatum, and reduced the host microglial response at the site of administration. These studies highlight the potential of biomaterials for delivering anti-inflammatory cytokines to the brain which could benefit brain repair strategies for Parkinson’s disease.

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Is the pH-sensitive receptor OGR1 expressed in neurons?

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OGR1 is a proton-sensitive GPCR that is ubiquitously expressed throughout mammalian tissues. Despite being linked to cancer, inflammation and hypoxia, OGR1 remains a relatively understudied receptor. At the mRNA level, OGR1 is thought to be expressed in the peripheral and central nervous system and in the SH-SY5Y cell line. The aim of this research is to first evaluate OGR1-mediated signalling in a recombinant expression system and then to better elucidate OGR1 function in neurons. Receptor activation in HEK HA-OGR1 cells was demonstrated by increased intracellular calcium (live-cell FURA-2 based microfluorimetry) in response to acidic buffer treatment (physiological buffer pH 6.4). Live-cell calcium imaging was used to investigate proton-sensitivity in primary neuronal cells; cerebellar, cortical and hippocampal, and differentiated SH-SY5Y cells. Proton-mediated calcium transients specific to HEK HA-OGR1 cells (versus untransfected controls) were reproducible, Gq-dependent (YM-254890-sensitive) and required calcium release from intracellular stores (thapsigargin-sensitive). Publications to date have focused on IP₃ formation following OGR1 activation, but this data characterises OGR1-mediated calcium transients further downstream of the same pathway. Despite being reported expressors of endogenous OGR1, SH-SY5Y cells did not elicit proton-sensitive calcium transients even following IGF-1 differentiation. Similarly, primary neuronal cells (cerebellar, cortical and hippocampal) did not show proton-sensitive calcium transients. The HEK HA-OGR1 overexpression system described in this study offers a valuable model for investigating this novel receptor. OGR1-mediated calcium transients are reproducible and dependent on the Gq-pathway. Results suggest that cerebellar, cortical and hippocampal neurons do not show any indication of proton-mediated calcium transients (pH 6.4) under resting conditions.
Event related potentials predict inhibitory control

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Currently, the relationship between individual differences in inhibitory control and electrophysiology is inconclusive. This may be due to small sample sizes and the high dimensionality of electroencephalography (EEG) data, which can cause both false positive and false negative findings. The application of machine learning methods provides one strategy for improving reproducibility in neuroscience. We aimed to investigate the predictive power of the EEG signal across spatial and temporal domains for inhibitory control using machine learning. We analyzed data from the stop-signal task, collected under EEG, in which a stop signal prompted the participant to withhold an already-prepared movement. Individual differences in inhibitory control were quantified via the stop-signal reaction time (SSRT). A machine learning method, penalized regression, was used to interrogate data from 64 scalp electrodes at 4 ms resolution (i.e. keeping a high spatial and temporal resolution). Using internal validation on a dataset collected from 148 participants, there was a cross-validated Pearson’s r of 0.27 between the predicted and the measured SSRT. The application of this model to an external validation dataset of 97 participants produced a Pearson’s r of 0.25. Spatio-temporal features overlapping well-known ERP components were predictive of the SSRT: the N2 in right frontal areas, the P3 in fronto-medial areas but in addition several early ERPs (<200 ms) were predictive. Individual differences in inhibitory control can be reproducibly found by applying machine learning to electrophysiological data.

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Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors. There is evidence for their involvement in pain and cognition, however, their role in pain-fear interactions is unknown. The basolateral amygdala (BLA) plays a key role in pain, conditioned fear and fear-conditioned analgesia (FCA). This study investigated the effects of systemic or intra-BLA administration of PPARα, PPARαδεδεδ and PPARα antagonists on formalin-evoked nociceptive behaviour, FCA, and conditioned fear in the presence and absence of nociceptive tone in rats. Male Sprague-Dawley (SD) rats received footshock in a conditioning arena. 23.5 hours later, rats received intraplantar injection of formalin into the right hind paw and intraperitoneal administration of vehicle, PPARα, PPARαδεδ or PPARα antagonists before re-exposure to the conditioning arena for 15 minutes. Nociceptive and fear-related behaviours were assessed and tissue levels of neurotransmitters/endocannabinoids measured in the BLA and central amygdala (CeA). In following experiments, male SD rats underwent the same FCA protocol; after intra-plantar formalin or saline administration, antagonists at PPARα, PPARαδεδ, PPARαδεδ, or vehicle, were microinjected bilaterally into the BLA and their effects on pain- and fear-related behaviours were assessed for 30 minutes. Systemic administration of PPARα PPARαδεδ and PPARαδεδ antagonists potentiated context-induced freezing without altering nociceptive behaviour. Systemically administered PPARα and PPARαδεδ antagonists increased GABA levels in the contralateral BLA and PEA levels in the ipsilateral CeA of FC rats. Intra-BLA administration of PPARα or PPARαδεδ antagonists potentiated context-induced freezing in the presence of pain. The three antagonists increased freezing time in the absence of pain in non-fear-conditioned rats. PPARs, and particularly PPARα and PPARαδεδ expressed...
in the BLA, may play a role in the short-term extinction of conditioned fear in the presence of nociceptive tone but do not appear to mediate FCA.

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Classification of alzheimer’s disease, mild cognitive impairment and healthy adults using EEG spectral power


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Mild Cognitive Impairment (MCI) is a disorder characterised by cognitive deficits greater than expected for a person’s age. MCI is considered to be a prodromal stage for Alzheimer's disease (AD). Between 20-40% of MCI patients will go on to develop AD or other dementia. Early detection of MCI is vitally important for enhancing diagnostics and care for individuals at increased risk for AD. Our goal was to investigate whether EEG spectral power (1-45 Hz) could be used to accurately classify participants into adults with AD, MCI and healthy controls. We also aimed to identify specific features of the EEG power signal associated with MCI and AD. Participants were patients with AD, MCI and healthy controls (n = 111 per group). Eyes open (EO) and eyes closed (EC) resting state EEG data (3 minutes each) were recorded from 30 scalp electrode sites. Absolute power and relative power values were calculated from 1-45 Hz. A machine learning method with penalized regression was then used to interrogate the EEG data. Classification accuracy will be evaluated separately for EO and EC conditions using both absolute and relative power values to determine the best predictor of group status. In addition, EEG features that best predict group membership will be identified (i.e. frequencies at specific scalp locations that are associated with MCI and/or AD status). Results will indicate the efficacy of EEG spectral power as a means of classifying AD, MCI and healthy individuals. Applying machine learning to EEG data in this way may provide a useful tool for helping to identify people at risk of developing AD.

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There is a growing recognition of the involvement of the gastrointestinal microbiota in the homeostasis of brain physiology and behaviour. Bacterial-derived metabolites play a central role in this communication, of which short-chain fatty acids (SCFAs) are perhaps the most studied. SCFAs have already been shown to play a pivotal role in gut function, host metabolism and immune system functionality. All these factors have previously been demonstrated to be adversely affected by psychological stress. We aimed to investigate whether SCFAs could alleviate stress-induced deficits in mice, specifically in reward-seeking behaviour, stress-responsiveness and intestinal permeability. We tested these parameters by administering a mix of the three principal SCFAs, (acetate, propionate and butyrate) dissolved in drinking water. One week after SCFA administration, mice underwent a three-week psychosocial stress intervention, followed by a behavioural analysis assessing reward-seeking behaviour, stress-responsiveness and intestinal permeability. We investigated the expression of genes associated with these behaviours using qRT-PCR. We have found that SCFAs alleviate the stress-induced increase in anhedonia in the female urine sniffing test. In addition, psychosocial stress increased stress-responsiveness in the stress-induced hyperthermia test with increased corticosterone following an acute stressor, both of which were ameliorated by SCFAs. We further found that SCFAs could downregulate corticotropin-releasing hormone (Crh) and mineralocorticoid receptor (Mr) expression in the hypothalamus, as well as hippocampal Mr expression. In addition, mice previously undergoing stress also showed increased in-vivo intestinal permeability. In the colon, gene expression analysis revealed that stress increased Mr expression, which was significantly ameliorated by SCFAs.
In conclusion, we have found that SCFA supplementation in mice undergoing psychosocial stress alleviates deficits in anhedonia, stress-responsiveness and the molecular architecture of the intestine.

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Postural Control as a measure of Neurodegeneration in FMR1 Carriers

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FragileX associated tremor/Ataxia syndrome (FXTAS) is a neurodegenerative movement disorder experienced by up to 40% of FMR1 premutation carriers over 50 years ([1]). However, it is not understood why only this proportion of carriers develop the disorder. Recently, subtle cognitive and balance impairments have been found in younger carriers without FXTAS, which may reflect progression towards disease onset. This study aims to identify sway parameters that are most sensitive to differences in postural control between carriers and control subjects, and which may be indicative of the progression towards FXTAS. Traditional sway parameters and sway complexity of 12 premutation carriers and 15 controls were measured using a force platform, under four conditions: standing with eyes open, closed and while engaged in an attention-based task (SART) and working memory task (N-Back). Traditional sway parameter included area, length, and velocity, and sway complexity was divided into directional subcomponents: anterior-posterior (AP) and mediolateral (ML). There were no significant difference between groups in sway area, length or velocity during each condition (p>0.05). Carrier’s ML complexity was significantly lower than that of the Carrier’s during both dual-tasks (SART: p=0.038, N-back: p=0.004) and remained consistent across tasks. The control group’s AP complexity increased during the SART (p=0.01) and N-back tasks (p=0.009) as well as ML complexity (p=0.001 for both tasks). There was, however, a negative correlation between age and complexity for the carrier group (p=0.01) that was not seen amongst controls. Carriers exhibited lower complexity during dual-tasks, suggesting capacity interference and inefficient division of attention between tasks. This reduced complexity reflects diminished capacity to adapt to increased cognitive demand [2]. The correlation between age and complexity may indicate an age-related decline in functionality which would advocate the use of complexity-based measures.
as clinical markers of neurodegeneration in premutation carriers, and a tool for monitoring progression towards disease onset.

**Gene co-expression analysis of the human substantia nigra identifies BMP2 as a novel neurotrophic factor for axonal neuroprotection in Parkinson’s disease.**

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The factors regulating the maintenance of human midbrain dopaminergic (mDA) neurons are largely unknown. Identifying these is important given the progressive loss of mDA neurons from the substantia nigra (SN) in Parkinson’s disease (PD). The aim of this study was therefore to identify novel neurotrophic factors functionally associated with human mDA neurons. We performed a co-expression analysis to identify all genes that had a significant correlation with tyrosine hydroxylase (TH) expression in the human SN. This screen identified a significant correlation ($p = 2 \times 10^{-4}$) between the neurotrophic factor, bone morphogenetic protein 2 (BMP2) and TH. We hypothesised that BMP2 plays a functional role in promoting the survival and axonal maintenance of human mDA neurons. As we have used open source transcriptome data (GSE: 60863) and human SH-SY5Y cells, which are a widely used model of human mDA neurons, no ethical approval was required. To test this hypothesis, SH-SY5Y cells were cultured in the presence of an empirically optimised concentration of 50 ng/ml BMP2 with/without the mDA neurotoxins 6-OHDA (15µM), MPP⁺ (1mM) and wild type (WT) or mutant α-synuclein for 72h. Immunocytochemistry confirmed that SH-SY5Y cells expressed the BMPR2 and BMPR1B receptors and Smad effector molecules, required for BMP2 signalling. Treatment with BMP2 for 72h significantly promoted neurite growth ($p<0.0001$) in SH-SY5Y cells. Additionally, we found that BMP2 completely protected against MPP⁺ and 6-OHDA. Importantly, given that α-synuclein-induced axonal degeneration is central to mDA axonal degeneration, we found that BMP2 also protected cells from both WT and mutant (A53T) α-synuclein-induced axonal degeneration. In summary, this data shows that BMP2 can protect axons from neurotoxin-induced degeneration in a model of human mDA neurons. Given that axonal degeneration is now recognised as a
crucial neuropathological event in PD, these findings are an important first step in rationalising the further study of BMP2 as a novel therapy for PD.

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Class-IIa HDAC inhibitors protect against MPP⁺-induced neurotoxicity in models of human midbrain dopaminergic neurons

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Parkinson’s disease (PD) is a neurodegenerative disorder characterized by progressive motor impairments due to the degeneration of midbrain dopaminergic (mDA) neurons. The early stages of the PD are characterized by progressive loss of mDA axonal terminals in the striatum. The lack of neuroprotective therapies means there is an intensive research effort aimed at identifying new therapies, in particular drugs that can cross the blood-brain barrier. Given that global alterations in histone acetylation have been reported in PD, a number of FDA-approved pan-histone deacetylase inhibitors (HDIs) have been tested as a neuroprotective agents. However their clinical utility is limited due to their lack of specificity. Here we sought to determine whether a class-IIa specific HDI known as MC1568, could protect against the neurotoxic effects of 1-methyl-4-phenylpyridinium (MPP⁺), which is a widely used dopaminergic neurotoxin. This study was performed under full ethical approval. To test our hypothesis, we used human SH-SY5Y cells which were treated for 72h with MC1568 (0.0001µM-10µM), or E14 rat VM primary cultures established from rat embryos obtained by laparotomy under terminal anesthesia. These were treated for 24h (20-100nM) and cultured with or without 1mM MPP⁺. Image J was used to quantify neuronal arbors and we found that MC1568 significantly promoted neurite growth (p<0.0001) in SH-SY5Y and tyrosine hydroxylase (TH)-stained mDA neurons (p<0.0001). To confirm that MC1568 promoted histone acetylation, both cultures were stained for acetylated histone 3 (acH3) which was quantified using Image J. MC1568 led to significant increases (p<0.0001) in acH3 in both cell types. Moreover, MC1568 could protect against MPP⁺-induced neuritoxicity in both models. In conclusion these data show that a class-IIa specific HDI exerts neuroprotective effects in two in vitro models of human mDA degeneration. This is an important first step in rationalizing the further study of class-specific HDIs as neuroprotective therapies in PD.
Optimisation of a glycan-functionalised collagen hydrogel for ventral mesencephalic cells delivery

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Parkinson’s Disease (PD) is a neurodegenerative disorder characterised by the death of dopaminergic neurons in the substantia nigra, which relates to different movement disorders. Currently there are only symptomatic therapies available and none of these address the specific pathophysiology of the disease. Collagen hydrogels have shown potential as a vehicle for delivery of cells into the brain, namely ventral mesencephalic (VM) embryonic cells, protecting them from the host environment and maintaining their viability. Additionally, their therapeutic potential can be further expanded by functionalising them to address a specific aspect of PD pathology, namely the glycosylation patterns altered upon onset of the disease. To develop and optimise a glycan-conjugated collagen-based hydrogel that will encapsulate and modulate the differentiation and sugar expression of VM cells in order to mimic the healthy brain glyco-environment. In this study, maltose, lactose and 2’-fucosyllactose were conjugated to collagen through a reductive amination reaction. These compounds were chemically characterised and glycan-collagen microgels were fabricated (2mg/ml of collagen and 0.2 and 0.4mM of crosslinker (4S-StarPEG)). Their cytotoxicity was assessed through alamarBlue® and PicoGreen® assays and their effect on VM cells differentiation and sugar expression was evaluated through immunostaining and lectin staining respectively. It was shown that the functionalisation has a yield of 50% which allows the remaining free amines to be crosslinked by 4S-StarPEG. At the cellular level, it was seen that the conjugates with maltose downregulated the astrocytic expression up to two weeks. Fucosylation was decreased and the sialylation increased in the group in contact with the maltose conjugated collagen. In this study, collagen was successfully functionalised with different disaccharides and their properties were investigated. The results suggest the influence of the conjugates on the cellular sugar expression and thus have potential applications as modulators of cell delivery system in the brain.
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Viral mediated neuroinflammatory priming exacerbates α-synuclein aggregate-induced neuroinflammation and degeneration: Implications for viral etiology in Parkinson’s disease

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Although the etiology of idiopathic Parkinson’s disease (PD) remains unknown, evidence suggests that PD may manifest after a lifetime of environmental exposures, including viral infection¹, interacting with underlying genetics. The aim of this study was to determine the effect of viral priming (using the synthetic dsRNA viral mimetic Poly I:C) on α-synuclein aggregate-induced neuropathology (induced by the small peptidomimetic FN075²,³) ex vivo in primary neural cultures and in vivo in rats. Ex vivo, neural cultures were prepared from the developing rat ventral mesencephalon and treated with Poly I:C (20 µg/ml) for 24 hours prior to treatment with FN075 (25 µM) for 48 hours. In vivo, 32 male Sprague-Dawley rats received unilateral intra-nigral injection of Poly I:C (30 µg) or vehicle, followed two weeks later by a subsequent unilateral intra-nigral injection of FN075 (1.93 µg) or vehicle. The effect of viral-like priming was assessed using immunostaining/immunoblotting for filamentous α-synuclein, dopaminergic degeneration, synaptic integrity, and neuroinflammatory markers. Motor behaviour was measured every two weeks after FN075 injection. Relative to the vehicle or single exposure, viral-like priming in combination with α-synuclein aggregation led to significant motor impairment, which was underpinned by the significant exacerbation of neuroinflammation and over 30% dopaminergic neuronal death in the substantia nigra. Dual exposure was also found to be associated with changes in synaptic markers ex vivo and in vivo. This study has demonstrated that viral mediated neuroinflammatory priming can dramatically enhance the consequences of α-synuclein aggregate formation in the nigrostriatal pathway, lending further support to the growing evidence that suggests viral infections are involved in PD etiology.
Addictive substances activate the reward circuitry in the brain, specifically the mesolimbic dopaminergic neurons originating in the ventral tegmental area projecting to the nucleus accumbens and other limbic structures including the dorsal striatum (DS), hippocampus, amygdala (Amyg) and regions of the prefrontal cortex. Chronic exposure to drugs like cocaine alters gene expression and produces long-term changes in such neural networks to underlie compulsive drug seeking and taking. One of the relatively persistent changes is the accumulation of ΔFosB, a highly stable variant of the FosB protein, in the NAc and connected brain circuitry. Targeting the molecular and transcriptional changes underlying alterations in behaviour, mood and cognition associated with persistent drug use may decrease the long-term risk of relapse. Psychedelic drugs produce strong subjective effects including changes in thought, mood, and perception. Beneficial effects have been reported in clinical trials of various serotonergic (5-HT) psychedelics in the treatment of mood disorders, including addiction. However, little is understood regarding the mechanism through which these drugs are mediating their benefits. For this study we used the psychedelic 5-methoxy-N,N-dimethyltryptamine (5-Meo). 5-Meo is a 5-HT receptor agonist at 5-HT-1A, 5-HT-2A and 5-HT-2C receptors. The aim of the study was to investigate molecular changes induced by 5-Meo in mesolimbic circuitry following chronic cocaine exposure. 5-Meo was able to reverse changes induced by repeated cocaine administration, including restoring expression levels of ΔFosB in the DS and Amyg to levels seen in saline-treated animals. The findings are discussed in the context of the use of psychedelics as treatments for addiction.
A network model of myelin plasticity

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Numerous studies in recent years have revealed compelling evidence that oligodendrocytes (OLs), the myelinating glial cells of the central nervous system, provide more than just electrical insulation to increase the velocity of action potential propagation. Controlled experiments have confirmed their role in remodelling neural circuits to facilitate learning and advances in imaging technology strongly suggest they have a role in the modulation of conduction delays to ensure coherent brain functioning. Despite the overwhelming evidence of mutual signalling between OLs and axons, the precise biological nature of the signalling remains unclear. Nevertheless, a network analysis reveals significant insights into the topological properties of any such coupling. Our aim is to 1) construct a plausible network based on the morphological features of OLs and the axons they myelinate and 2) demonstrate that varying myelin content along an axon can naturally synchronise the phase and arrival times of heterogeneous oscillating signals. A simple network is constructed with neurons as nodes and OL processes as edges. The Kuramoto coupled oscillator model, adapted to include time delays and a myelin optimisation component, evolves on this network. A static network of interacting neurons and OLs is constructed. A dynamic model of myelin plasticity on this network reveals that for a wide interval of random oscillator frequencies and random arrival times at a mutual target, both the signal phase and signal arrival times are synchronised. We have shown that neuron-glial interactions can be included in a plausible neural network model that replicates some of the main qualitative features of myelin plasticity. The scope for glial cells to modulate neural processing is emphasised and it is hoped that more detailed models will be developed that explicitly include neuron-glial connectivity.

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Per Pass histological analysis of thrombotic material for the characterization of heterogeneity within Acute Ischemic stroke clots

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Stroke is the leading cause of disability in the Western world and the third most common cause of death. Acute ischemic stroke (AIS) represents approximately the 85\% of all strokes and is caused by clots that obstruct blood vessels supplying the brain. The characterization of blood clots obtained by thrombectomy from patients affected by AIS is an emerging area of research. Often, as clot fragments are being removed, some of the clot is removed relatively easily, but the remainder may take multiple passes. We aim to study the heterogeneity within clots in order to gain an understanding of the composition of the most difficult ones. To date, more than 200 cases have been collected from two European partner hospitals in Dublin and Gothenburg. Histological analysis using Haematoxylin & Eosin (H&E) and Martius Scarlet Blue (MSB) stain has been performed using Orbit Image Analysis. Within the initial 50 cases analysed using the specimens received from two partner hospitals, 11 cases (22\%) required multiple passes to successfully remove the clot. Our initial results have shown that clot fragments that are difficult to remove have increased platelet and fibrin composition, together with a reduction in red blood cells percentage. According to the preliminary data, a trend in within-clot heterogeneity has been observed in the cases that require multiple passes for their successful removal. Their characterization will be helpful to advance therapeutic approach, especially for the most difficult cases.

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Resting state functional connectivity in the infant brain using data from the developing human connectome project (dHCP)

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Functional connectivity magnetic resonance imaging (fcMRI) of neonates allows us to establish how early brain organization relates to subsequent development. We studied brain functional connectivity with rs-fMRI in healthy full term (FT) neonates using data from the developing human connectome project (dHCP) to characterise early development in the neonate brain. Our objective was to assess brain functional connectivity in healthy, term newborns (n = 34). A total of 34 healthy neonates from the dHCP (21 males, 13 females; gestational age range, 36.86 – 44.14 weeks; mean gestational age, 39.85) were included in this study. Image processing was carried out using Statistical Parametric Mapping software (SPM8: Welcome Trust Centre for Neuroimaging, London, UK). After pre-processing, data were analysed using a seed-ROI based method. Ninety cortical and sub-cortical ROIs were defined using an Automated Anatomical Labelling (AAL) atlas mapped to neonates (Shi et al., 2011). Brain functional connectivity analysis were performed using SPM8 and the Functional Connectivity (CONN) toolbox. The BOLD time series for multiple seed regions was cross-correlated with all other voxels in the brain, generating correlation maps identifying regions with functional connection to the region of interest. Correlation coefficients were transformed according to Fisher z-transformation to improve for normality. Multiple networks demonstrating temporally correlated BOLD signal were identified. These neural networks were identified using seeds located in the sensorimotor, medial and lateral prefrontal and temporal cortices. Limited correlation between left and right hippocampi (r = 0.202, p >.05) was found. Our analysis reveals different contributions of FC in different regions of the brain. High correlation observed in FC of sensorimotor and visual areas may reflect the importance of binocular vision in neonates as their coordination in generating body movements is developed. Lower correlation in hippocampal
areas may be explained by their association with integrating sensory experiences and higher cognitive processes. This study has implications for understanding how the immature brain develops.

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Identifying a biological signature of vulnerability to prenatal maternal stress: implications for infant neurodevelopment

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It is well known that maternal stress during pregnancy can incur adverse neurodevelopmental outcomes in the offspring. Such stress has been shown to increase gastrointestinal (GI) permeability, potentially via actions on the gut microbiota, leading to bacterial components entering circulation and inducing a low-grade inflammatory state. This in turn may lead to alterations in tryptophan metabolism along the kynurenine pathway which evidence suggests can impact negatively on neurodevelopment. This study aims to investigate whether stress during otherwise healthy pregnancies elicits a biological signature which can be used to infer enhanced liability to psychopathology in the offspring. A healthy cohort (N = 105) of nulliparous female participants with singleton pregnancies were utilised in the analysis. Self-reported assessments of stress using validated questionnaires were used to stratify this cohort into equally matched high and low stress groups. Plasma samples were collected during the first (15 weeks) and second (20 weeks) trimesters of pregnancy. Markers of GI permeability (Intestinal Fatty Acid Binding Protein (IFABP); Lipopolysaccharide Binding Protein (LBP); Soluble CD14) and pro-inflammatory cytokines (IFNγ; TNFα; IL-6; IL-8; IL-18) were assessed by Enzyme-linked Immunosorbent Assay (ELISA), while plasma tryptophan and kynurenine concentrations were determined using High Performance Liquid Chromatography (HPLC). Preliminary results suggest that circulating markers of GI permeability are influenced by high levels of prenatal maternal stress. Whether such influences translate to a pro-inflammatory response that remodels the direction of tryptophan metabolism is currently under investigation. Our findings demonstrate the potential for markers of GI
permeability to inform suitable intervention strategies aimed at counteracting the effects of prenatal maternal stress either via stress reduction techniques or microbiota targeted nutritional approaches.

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Machine learning to predict outcomes and functionality in adolescents with psychotic experiences

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It has been shown that children and adolescents who experience psychotic symptoms are at increased risk of psychosis later in life. Establishing early predictors of later psychosis is therefore a highly desirable goal as it provides both potential clinical value and insight into the etiopathophysiology of psychosis. A cohort of 212 children was interviewed as part of a longitudinal study to follow the outcomes of children with psychotic experiences. This project used a subset of data from that study, examining the clinical and cognitive data of 165 participants collected at 11-12 years of age. The dataset was analysed via a machine-learning algorithm in order to better detect subtle relationships and to contribute to a larger machine-learning project that will encompass the entire dataset. It was found that clinical measures of psychosis are highly associated with psychotic experiences and cognitive tests were found to be associated with functionality, suggesting external validity. Logistic regression identified a number of variables correlated to psychotic experiences for further investigation in the integrated model. Machine learning is a highly versatile tool for evaluating large and complex bioscience datasets. We found that machine learning models can replicate known outcomes and identify further variables for investigation as predictors of psychosis later in life.

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Internal spatial body configurations are crucial to successfully interact with the environment and to experience our body as a three-dimensional volumetric entity. These representations are highly malleable and are modulated by a multitude of afferent and motor information. Despite some studies reporting the impact of sensory and motor modulation on body representations, the long-term relationship between sensory information and mental representation of own body parts is still unclear. We investigated hand representation in a group of expert magicians who used sleight of hand as the main aspect of deception and in a group of age-matched adults naïve to magic (control group). Participants were asked to localise landmarks of their fingers when their hand position was congruent with the mental representation (Experiment 1) and when proprioceptive information was “misleading” (Experiment 2). Magicians outperformed controls in both experiments, suggesting that extensive training in sleight of hand has a profound effect in refining hand representation. Moreover, the impact of training seems to have a high body-part specificity, with a maximum impact for those body sections used more prominently during the training. Sleight-of-hand training may lead to a specific improvement of hand mental representation, which relies less on proprioceptive information.

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FKBP5 pharmacological inhibition as a novel strategy for the treatment of stress-related disorders: in vivo and in vitro approaches

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Stress-related psychiatric disorders are among the leading causes of morbidity and mortality. Considering that many individuals fail to respond to the available pharmacological therapies, there is a need for new and better antidepressants. Polymorphisms in the FK506-binding protein 51 (FKBP5), a co-chaperone of the glucocorticoid receptor, have been linked to antidepressant treatment response and susceptibility to stress-related psychiatric disorders. Although it’s been more than a decade since FKBP5 inhibition emerged as a potential novel antidepressant strategy, the antidepressant-like effects of pharmacological FKBP5 inhibitors and their effects on structural neuronal plasticity remain largely unexplored. The aim of this work was to evaluate the effect of an FKBP5 pharmacological inhibitor on neurite outgrowth in vitro and on depressive-like behaviour in vivo. For the in vitro approach, primary hippocampal neuronal cultures from E18 mice were treated for 48 h with different concentrations of a highly selective FKBP5 inhibitor. Compared to DMSO, the FKBP5 inhibitor (250, 500 and 1000 nM) increased both neurite outgrowth and dendritic branch points. Interestingly, treatment with 500 nM of the FKBP5 inhibitor produced greater increases in neurite outgrowth and dendritic branching than treatment with brain-derived growth factor (BDNF; 40 ng/mL). For the in vivo approach, the FKBP5 inhibitor (20 mg/kg) was administered to C57BL/6 male mice 16 h or 1 h prior to the forced swimming test and blood was collected for corticosterone measurement. Remarkably, the inhibitor decreased the immobility time of the mice when administered 16 h prior to the behavioural testing but not 1 h before and none of these changes were accompanied by alterations in blood corticosterone levels. Taken together, this data suggest that pharmacological inhibition of FKBP5 may be a novel strategy for the treatment of stress-related disorders and warrants further exploration.
The marine invertebrate *Pleurobrachia pileus* as a model organism in neuroscience

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While modern neuroscience research is dominated by a small number of model organisms, exploiting the greater diversity of neurobiology can allow key scientific questions to be asked with new model organisms. *Pleurobrachia pileus* is representative of phylum ctenophora with a nervous system composed of a decentralised polygonal network beneath the epithelial layer, distributed across the entire body wall. We demonstrate that this nerve net can be visualised in-situ with fluorescent immunolabelling with minimal distortion of the body wall, allowing characterisation of network structure in relation to each individual’s anatomy. We also demonstrate that these animals exhibit predictable and measurable behavioural responses to environmental stimuli. Specifically, mechanical stimulation to the body wall induces an escape swimming response, which can be characterised by video analysis of the motile cilia characteristic of this phylum. We have also characterised reflexive withdrawal of the feeding tentacles in response to changing water levels around the animal. To permit long term and year round studies we have developed a custom built kreisel aquarium system with automated feeding. To date, we have maintained ~100 animals collected in the Irish Sea for at least four months. The relationship between network architecture, information flow and behaviour may be studied in these animals While the phylogenetic relationships between ctenophores and other phyla is controversial, they either represent the earliest evolutionary origins of the nervous systems, or the only example of independent nervous system evolution. In either case, this species presents a unique opportunity to study fundamental questions of neuroscience.

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The relationship between depressive symptoms and sustained attention in an older adult population

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Our ability to selectively attend to information while ignoring irrelevant information is important for everyday functioning. Poor attentional control is thought to play a role in the development of depression and anxiety. This study aims to explore the relationship between depressive symptoms and sustained attention in an older adult population with the hope of clarifying whether depression and anxiety are co-occurring symptoms of cognitive impairment or independent risk factors. We specifically examined whether diminished attentional control is associated with increased depressive and anxiety symptoms. Participants were 75 healthy older adults (mean age = 66, SD = 5.2, 43 = female, 32 = male). Participants completed the Geriatric Depression Scale (GDS) and the Depression Anxiety Stress Scale (DASS) as measures of depressive and anxiety symptoms. As measures of cognitive performance, participants completed the Rapid Visual Information Processing (RVP) and the Reaction Time (RTI) components of the Cambridge Neuropsychological Test Automated Battery (CANTAB). RVP is a measure of sustained attention and RTI provides assessments of motor and mental response speeds, as well as measures of movement time, reaction time, response accuracy and impulsivity. Analysis is currently ongoing. This study will use a cross-sectional design. Results will help to elucidate whether depression and anxiety are co-occurring symptoms of cognitive impairment or independent risk factors. We in turn hope this will help to enhance the detection and treatment of affective symptoms in older people with cognitive impairment.

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EEG beta power: Investigating anxiety levels in healthy older adults

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Electroencephalographic (EEG) brain waves represent different cognitive states. The beta waveform (12.5-30Hz) typically occurs during wakeful consciousness and executive processes such as memory and attention. However, beta has also been associated with negative states such as anxiety and stress. Anxiety can compromise executive functions, and has been suggested as a predictor of future cognitive decline in older adults. The aim of the study is to investigate if there is a positive correlation between higher symptoms of anxiety in healthy older adults and resting state beta power, and if so, how this relates to cognitive performance. Sixty-one healthy older adults (mean age = 67.49, age range = 57-80) took part in this study. Resting state EEG was recorded from 128 scalp electrodes. Participants completed 5 minutes eyes-closed and 5 minutes eyes-open resting state recording. Symptoms of anxiety were assessed using scores from the anxiety subset of the Depression and Anxiety Stress Scale (DASS). Cognitive performance was assessed via Category and Letter Fluency word recall tasks. The analysis is in progress. Absolute and relative power values will be calculated for the beta frequency band and correlated with anxiety scores. We expect to see a positive correlation between symptoms of anxiety and beta power and a negative correlation between symptoms of anxiety and cognitive performance. Results will determine the potential utility of resting state beta power as a tool to monitor anxiety levels in healthy subjects. Results may also inform ongoing research into whether EEG measures can be used to identify potential pathology in healthy populations and facilitate early intervention.

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Caesarean-section delivery induces behavioural changes in adulthood, reversed by synbiotic treatment

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The prevalence of caesarean section delivery has been increasing over the last number of decades with rates at an all-time high. C-section has also been linked to altered microbiota composition compared to vaginal delivery. Gut microbiota composition has been linked numerous psychiatric disorders and treatment with live bacteria (probiotics) and dietary fibre that encourages growth of beneficial bacterial strains (prebiotics) has been shown to be beneficial in a number of these situations. The aim of this project was to determine if mice delivered via caesarean section would have a disrupted microbiota and altered behaviour compared to vaginally delivered animals. We then sought to investigate whether treatment with a synbiotic (prebiotic and probiotic combination) or disruption of the microbiota through antibiotic administration could modify these behavioural changes. NIH Swiss mice were delivered either vaginally or via caesarean section and maintained in their home cage with their litter and mother (or foster mother in the case of c-section delivery). Following weaning animals were provided with either standard chow or a probiotic diet. Additionally, all animals were gavaged with either saline or probiotic mixture. At eight weeks of age animals underwent a behavioural battery to assess for sociability, cognition, anxiety and depressive-like behaviours. Animals were culled and brain tissue collected for analysis with cecum also collected for microbiota analysis. The experiment was then repeated with the mothers receiving Animals delivered via C-section displayed increased anxiety in the elevated plus maze, altered cognitive behaviour in the Novel object recognition task, as well as altered social recognition in the three-chamber sociability test. Treatment with synbioitcs was able to reverse changes in anxiety and sociability. Further analysis of behaviour is ongoing as well as analysis of antibiotic-treated animals and analysis of gut microbiota composition. C-section delivery causes increased anxiety and decrease social recognition in mice in adulthood, treatment with a combination of pre- and probiotics able to reverse these changes. These results suggest that microbiota
alteration in early-life can affect behaviour in adulthood. We suggest that a synbiotic treatment may be of use in reversing behavioural differences induced by early-life microbiota alterations.

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Ionic stimulation and inhibition of adhesive release from the neurally derived colloblast cells

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The marine invertebrate phylum Ctenophora has been under scrutiny for its potential independent evolution of a nervous system. A feature of tentacular ctenophores is their long tentacles covered in adhesive colloblast cells. Recent developmental and genomic evidence has proposed these cells are derived from neuron progenitors, and thus may be evolutionarily derived from neurons also. This research aimed to identify whether colloblast adhesive release was analogous to neurotransmitter release by studying the ionic influence over adhesive release. Artificial sea water (ASW) solutions of varying calcium, magnesium, sodium, and potassium concentration (but always the same tonicity and osmolarity) were applied to severed tentacles. The effect of the solutions on the tentacle/colloblasts was observed microscopically using oblique illumination microscopy. Solutions of high calcium (>26.9 mM Ca²⁺) were found to be stimulatory for adhesive release. This was observed by the formation of large vesicles on the surface of the tentacles, along with blurring of the colloblast morphology. High calcium ASW also induced colloblast extension, indicating an additional step in control over adhesive release. High potassium ASW was also found to be both stimulatory (adhesive release and muscular contraction) and deadly to the tentacle fragments (complete paralysis). Calcium-free ASW and sodium-free ASW were both found to induce relaxation of tentacular muscle and did not trigger any kind of adhesive release phenotype. The colloblast cells are responsive to external application of high calcium and high potassium solutions and behave in a way that would be expected if calcium influx and potassium influx are triggers of adhesive release. Potassium stimulating adhesive release may indicate neural activation inhibiting adhesive release, while calcium stimulation suggests the potential for calcium influx triggering adhesive vesicle fusion with the membrane.

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The encapsulation of primary dopaminergic neurons in a GDNF-loaded collagen hydrogel significantly improves their survival and function after transplantation into the Parkinsonian rat brain

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The use of primary dopaminergic neurons for neural transplantation has not yet reached a level to justify its use as a routine therapeutic procedure, largely due to limitations in cell survival, with only ~5% of cells surviving the transplantation process. Injectable biomaterial scaffolds have the potential to improve graft survival and function by providing a physical substrate into which pro-survival factors can be complexed. Therefore, the aim of this study was to determine the effect of a GDNF-loaded collagen hydrogel on the functionality of primary dopaminergic neurons implanted into the striatum of the 6-hydroxydopamine-lesioned rat. Rats were given a unilateral intra-MFB 6-hydroxydopamine lesion prior to transplantation. Two weeks later, a single cell suspension was derived from the ventral mesencephalon (VM) of E14 or E12 rat embryos, encapsulated in the collagen hydrogel or control transplantation media with or without GDNF (1000ng), and transplanted into the lesioned striatum. Functional recovery was assessed at three week intervals post-transplantation for 12 weeks using amphetamine-induced rotations. In line with expectations, we found that the VM transplants from both embryonic donor ages reduced amphetamine-induced rotations in all groups. However, the groups in which the VM cells were encapsulated in the GDNF-loaded collagen hydrogel showed a significantly greater level of recovery. Post-mortem analysis shows that the delivery of VM cells in a GDNF-loaded hydrogel significantly reduced the host immune response to the transplanted graft, increased the number of surviving dopaminergic neurons by 5-fold and the volume of striatal re-innervation by 4-fold. In conclusion, this study provides further evidence of the potential of biomaterials as matrices for cell transplantation into the brain. By providing a physical substrate into which pro-survival factors, such as GDNF, can be complexed, they can improve the functional outcome of dopamine cell replacement in the brain.
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Intrinsic sex differences in hippocampal neurogenesis and its regulation by the stress hormone corticosterone

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Stress, particularly during early life, is a major risk factor for the development of major depression. Depression is twice as prevalent in women compared to men, which suggests that biological sex is also a determining risk factor. In animal models, stress during early life can induce depressive-like behaviours and negatively impact neurogenesis in the hippocampus, a brain area important in the regulation of the stress response. Evidence suggests that sex may modulate the impact of stress on adult hippocampal neurogenesis, however it is unknown whether these differences are cell-intrinsic or depend on the actions of sex hormones which become more pronounced after puberty. We aimed to determine whether sex differences in response to the stress hormone corticosterone are apparent in the absence of sex hormones prior to the onset of puberty. To this end, we evaluated the impact of corticosterone on proliferation and differentiation of hippocampal neural progenitor cells (NPCs) derived from pre-pubertal males and female Sprague-Dawley rats in vitro. NPCs were exposed to corticosterone and cultured in media promoting either cell proliferation (acute exposure, 4 hours) or neuronal differentiation (chronic exposure, 7 days). Corticosterone significantly decreased both cell proliferation and neuronal differentiation compared to the vehicle control. However, the effect of corticosterone was more pronounced in cells derived from males than females. The results suggest a sexually dimorphic response of hippocampal NPCs to corticosterone in the absence of circulating sex hormones in vitro. However, it is unclear whether the same trend applies at different stages of development, such as post-puberty. It will also be important to determine how this differential sensitivity to corticosterone relates to behavioural responses to stress in males and
females and contributes to risk for developing stress-related psychiatric disorders.

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Atlas-based and manual diffusion tractography of the fornix – a comparison of techniques

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The fornix is a white matter tract integral to the limbic system of the brain. Diffusion weighted imaging has recently been used to isolate and quantify this structure in vivo. Atlas-based tractography has been used to isolate tracts from whole brain tracts using a whole brain approach. No study to date has evaluated automated approaches to calculating and reconstructing this tract from diffusion imaging. The aim would be to evaluate an atlas-based protocol for isolating the fornix from whole brain tracts. Diffusion imaging and subsequent whole brain tractography were performed on 102 subjects as part of the REDEEM Depression study in TCD. Tractography was executed using ExploreDTI software. Manual tractography involved mapping out a set of standard gates onto the brain of each subject which produced a fornix. This procedure was repeated independently by four trained raters. In atlas-based tractography, the same set of standard gates were drawn onto the brain of a random average subject which acted as the template. Automated placement of gates was calculated with reference to the template subject. Manual and atlas-based fornices were compared in terms of robustness of the tracts and tract metrics. All raters had good reproducibility of the fornix using standard gates. Atlas-based tractography was comparable to gold standard manually drawn tracts, but with some limitations (over and under inclusion of streamlines). Comparable to previous studies looking at major white matter
tracts, atlas-based tractography showed promising results in terms of drawing the fornix. Further research needs to be carried out in order to improve and fine-tune the gates used to attain the most accurate representation of this complex limbic tract. Automated tractography may allow fast and efficient calculation of this under researched yet significant area and could have an important clinical potential.

**Molecular mechanisms underlying depression in chronic inflammatory diseases**

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The serotonin transporter (SERT) facilitates high affinity reuptake of 5-HT from the extracellular fluid. Dysregulation of transporter function has been implicated in a range of mood disorders including depression. Recent studies have linked immune system dysfunction to both depression and to altered serotonin transporter activity. The aim would be to investigate the effect of chronic inflammation in a mouse model on behaviour and neuronal SERT activity and identify sex specific effects in this model. Our lab has used collagen induced arthritis (CIA) in mice, a model of chronic inflammatory disease to investigate the effect of prolonged inflammation on brain SERT function and behaviour. We found that male CIA mice show depression-like behaviour that is temporally correlated with a region-specific upregulation of SERT activity in the hippocampus. SERT activity enhancement occurs at a post translational level and is independent of SERT trafficking. Furthermore, we have shown that treatment with the anti-TNFα drug Enbrel can prevent both the behavioural symptoms and the increase in hippocampal SERT activity in the hippocampus of CIA mice, suggesting a pivotal role for TNFα signalling in SERT regulation in this disease model. Our study provides novel insight into the molecular mechanisms underlying depression in chronic inflammatory diseases in humans, with particular relevance to rheumatoid arthritis.
Papez’s forgotten tract: 80 years of unreconciled findings concerning the thalamocingulate tract

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The thalamocingulate tract is a key component of the Papez circuit that connects the anterior thalamic nucleus to the cingulum bundle. Although the other white matter connections of the circuit were well defined in Papez’s original 1937 paper, the anatomy of the thalamocingulate pathway was mentioned only in passing. Since that time there has been a paucity of research describing its actual anatomical trajectory. In particular, the research describing how it interacts with the cingulum bundle is conflicted and has varied over time with changing methodologies and species of research subjects. Our unsuccessful attempts at locating and isolating this tract using diffusion tensor imaging gave impetus for a focused review of the literature. We sought to disaggregate the methodological and epistemological reasons for the lack of anatomical consensus regarding the thalamocingulate tract. To achieve this, we sought to employ a systemic approach to reviewing influential earlier anatomical dissection and neuronal tracing studies as well as contemporary diffusion magnetic resonance imaging studies of the thalamocingulate tract was undertaken across species. The primary objective of this research is to help establish that no consensus currently exists despite the existence of studies suggesting a description of the course of the tract, and to elucidate the reasons for this disagreement which may assist future research. This literature review was conducted using PubMed/MEDLINE, Google Scholar, EMBASE, The Cochrane Library, OVID and PsycINFO. Studies were identified with the keywords ‘thalamocingulate tract’, ‘anterior thalamic projections’, ‘thalamocortical radiations’, ‘anterior thalamic nuclei to cingulate cortex’, and ‘Papez circuit’. Resources such as older texts within the Anatomy Department of Trinity College Dublin and Trinity College Library were also consulted. References in all studies were checked and appropriate studies were identified. Studies that described the thalamocingulate tract using
anatomical dissections, neuronal tracing techniques or neuroimaging were included. Information pertaining to the course of the tract was examined with respect to methods, genus and the specific termination of the thalamocingulate fiber tracts. We found that although inconsistent, prior research broadly encompasses two distinguishable descriptions of how the anterior thalamic nucleus interfaces with the cingulum after passing laterally through the anterior limb of the internal capsule. The first group of studies found that the pathway turns medially and rostrally and passes to the anterior cingulate region (Brodmann areas 24, 33, and 32). A second group suggests that the thalamocingulate tract interfaces with both the anterior and posterior cingulate (Brodmann areas 23 and 31) and retrosplenial region (Brodmann area 29). Variance in the pathway appears to be a result of the complexity of the involved structures, the difficulty in discriminating between neural formations and methodological differences between anatomical dissection, neuronal tracing and diffusion studies. On balance this tract appears to be more than a simple single projection and may have multiple anatomico-functionally organized projections dependent on the exact subnuclei involved, the fiber terminations in the cingulum and the anatomical trajectory from the anterior thalamus.

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