33rd Annual Cambridge Neuroscience Seminar

CNS2023: INTERDISCIPLINARY INSIGHTS ON THE FUTURE OF DEMENTIA RESEARCH

Robinson College
26th September 2023
We are very pleased to welcome you to the 33rd Cambridge Neuroscience Seminar: “Interdisciplinary insights on the future of dementia research”. As the title suggests, we are using this opportunity to think about the future of dementia research at Cambridge. We aim to highlight the strength in the interdisciplinary approach to tackling dementia in Cambridge and how collaboration, with the communal aim of understanding these diseases and identifying new treatments, is key.

Last year, Cambridge Neuroscience launched its six new interdisciplinary Themes and now we are delighted to open our new and interactive website. Take a moment to explore the site, where you will find information on funding opportunities, credibility in neuroscience, equality, diversity, inclusion & wellbeing, early career researchers, history, in addition to a whole new postgraduate training portal, which will enable prospective students to learn about the amazing work we are doing and come and join us! You will also see that your new and improved profiles will enrich your interdisciplinary experience at Cambridge allowing you to seek new collaborations in just a few clicks. This is just a snapshot and so please do take some time to explore the site fully – including the wonderful potted history of neuroscience at Cambridge!

Cambridge Neuroscience is ever evolving and dynamic, with incredible researchers across multiple Schools, Departments, Institutes and Centres working together, committed to supporting new, multidisciplinary approaches to solving the mysteries of the brain. Collaboration is key and the discoveries, awards and successes of individuals are dependent on many – technical and administrative staff, college colleagues, students, post-doctoral researchers and other faculty members. Cambridge Neuroscience is its people, and we are very grateful to them. Please do get in touch if you have any ideas of how to shape a brighter and bigger future!

Thank you so much for joining us today – we are delighted to welcome our plenary speakers Professors Catherine Mummery and Sarah Tabrizi as our guests. Furthermore, we are grateful to all our speakers, chairs, poster presenters and data blitzers, poster judges, volunteers, exhibitors and sponsors and most of all to you, our membership!

Paul Fletcher
Ewan St John Smith
Dervila Glynn

Check out our website here
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Practical Arrangements:

Lectures: Auditorium theatre (15). You are also free to sit in the adjoining Auditorium lounge and view the talks in a more informal setting. Names badges must be worn at all times.

Lunch, posters and trade exhibition: The Dining Hall, Robinson College (12)

Drinks reception: 18:40, Robinson College Gardens

Dinner: 19:30, The Dining Hall, Robinson College, dress code is smart casual (pre-booking is essential)

Meeting organised by Dervila Glynn on behalf of Cambridge Neuroscience. We would like to thank all of our volunteers, especially our colleagues at CamBRAIN and all our local suppliers. Sponsors were not involved in the organisation of the meeting, selection of speakers, attendees or content.

Sponsors: We would like to thank all our sponsors for their generous support. Please take the time to go and visit their exhibits during the refreshment breaks.

We would like to thank the staff of Robinson College for their help in hosting CNS2023.

Twitter: @CamNeuro #CamNeuro2023
CNS2023 – Interdisciplinary Insights on the Future of Dementia Research
Robinson College | Programme
Tuesday September 26th 2023

08:00-08:55 Registration and refreshments

**Session One**
Chair: Ewan St John Smith, Pharmacology @psalmotoxin

08:55-09:00 Welcome
09:00-09:25 David Klenerman – Chemistry
Next generation diagnostics for neurodegenerative disease

09:25-09:50 Barbara Sahakian - Psychiatry
Achieving better brain health and wellbeing in older age and early detection of memory problems.

09:50-10:30 Opening Plenary - Cath Mummery - University College London
Emerging therapies in dementia: a new era

10:30-11:00 Coffee

**Session Two**
Chair: Janet Kumita, Pharmacology @jrkumita

11:00-11:25 Ben Underwood – Psychiatry
How can we improve clinical dementia care now and in the future?

11:25-11:50 Gabriele Kaminski-Schierle – Chemical Engineering & Biotechnology
Exogenous Tau affects intracellular organelle morphology and neuronal signalling

11:50-12:15 Benjamin Ryskeldi-Falcon - MRC Laboratory of Molecular Biology
Structures of pathological protein filaments in dementia

@psalmotoxin
@jrkumita
12:15-12:40  Hugh Markus – Clinical Neurosciences  
Vascular contribution to dementia- the neglected player
12:40-13:10  Early Career Data Blitz
13:10-14:40 Lunch, Exhibition and Poster Session

**Session Three**  
Chair: Maria Grazia Spillantini, Clinical Neurosciences  
@SpillantiniLab

14:40-15:05  András Lakatos – Clinical Neurosciences  
Novel human neural organoid models: interrogation of mechanisms and therapeutic possibilities in neurodegeneration in the multi-omics era
15:05-15:30  Leo Chouliaras – Psychiatry  
DNA methylation sequencing in Lewy Body Dementia
15:30-15:35  Bitsize overview of UK Dementia Research Institute at Cambridge  
Mina Ryten - UK Dementia Research Institute
15:35-15:40  Bitsize overview of The ALBORADA Drug Discovery Institute  
John Skidmore – The ALBORADA Drug Discovery Institute
15:40-15:45  Bitsize overview of NIHR Cambridge Biomedical Research Centre  
James Rowe – MRC Cognition and Brain Sciences Unit & Clinical Neurosciences
15:45-16:10  Shalom Henderson – MRC Cognition and Brain Sciences Unit & Clinical Neurosciences  
Language, brain and disorder - a search for simplicity
16:10-16:40 Afternoon break

**Session Four**  
Chair: Paul Fletcher, Psychiatry  
@PaulPcf22

16:40-17:05  Maura Malpetti – Clinical Neurosciences  
From brain scans to blood tests - multidisciplinary progress on inflammation in dementia
17:05-17:35  Tim Rittman/Zoe Kourtzi – Clinical Neurosciences/Psychology  
AI for better brain health - turning the hype into reality
17:35-18:00  Roger Barker – Clinical Neurosciences  
Can we realistically repair the brain in Parkinson’s?
18:00-18:40 Closing Plenary - Sarah Tabrizi - University College London  
New genetic therapies for Huntington’s disease - Challenges and opportunities
18:40-18:45 Closing Remarks, Prizes and Acknowledgements
18:45-19:30 Drinks and networking
19:30-21:30 Dinner
Cambridge Neuroscience is committed to doing our part to protect our environment and work towards carbon neutrality. Here are some things we are doing to make CNS2022 more sustainable.

**Our venue:**
We chose Robinson College to host CNS2023 – an Eco-Friendly venue who tirelessly work to fulfil their sustainability promise and an NUS Green Impact Platinum Award winner for the fourth year in a row - one of 8 Colleges in Cambridge that achieved this accolade! For more on Robinson College sustainability policy, please see: https://www.robinson.cam.ac.uk/college-life/sustainability-robinson-college

**Reducing Waste:**
- CNS 2023 is committed to going single use Plastic-Free
- We will not be using disposable crockery, cutlery or glassware
- We are using plastic free badges and are reusing signage where possible
- All food waste from Robinson College is composted
- Robinson College aim to maximise the proportion of waste that is recycled and minimise the quantity of non-recyclable refuse

**Reducing Water Use:**
- There will be an opportunity to refill your water bottle on site

**Sustainability:**
- We are choosing greener food & beverages. Our lunch and snack menus comprise of >60% plant-based food options.
- We are using Fair Trade products where possible (tea, and coffee) and seasonal flowers.
- We are using local businesses for our suppliers where possible (photography, cloth poster recycling, flowers and balloons!)

*Sustainability is the responsibility of all involved, each sector must make decisions at every step that support sustainable practices.*

**Here are some things you can do to further our sustainable effort**
1. **Think before you print a poster** - Perhaps you can reuse a previously printed poster or reuse this poster at a future conference.
2. **Repurpose your cloth poster** into a useful tote bag with Mouse & Bear (see below)
3. **Bring your own reusable water bottle**
4. **Consider how you will travel to CNS2023** - One local bus route services the College, namely, the U or Universal. The Universal bus service links Madingley Park and Ride and Eddington with West Cambridge, the railway station and the Cambridge Biomedical Campus (including Addenbrooke’s).
Dementia is an umbrella term for a range of progressive conditions that affect the brain, impacting 50 million people worldwide. Dementia damages the nerve cells in the brain so messages cannot be sent effectively, which prevents the brain from functioning normally. There are over 200 subtypes and causes of dementia, but the four most common are: Alzheimer’s disease, vascular dementia, frontotemporal dementia and dementia with Lewy bodies. Dementia can affect a person at any age, but it is more commonly diagnosed in people over the age of 65 years and the UK has an ageing population. The symptoms of dementia can include: memory problems, disrupted cognitive ability (processing information), difficulties with communication, changes in mood and behaviour.

Dementia research has made phenomenal advances over the last couple of decades, with many of the major discoveries made by researchers at Cambridge, some of which are described here. In Alzheimer’s disease, work done in Cambridge was the first to show that the microtubule-associated protein tau is the major component of the filaments that form the neurofibrillary tangles in Alzheimer’s disease and other tauopathies. Cambridge neuroscientists also discovered that alpha synuclein is the major component of Lewy bodies, the characteristic aggregates of Parkinson’s disease. The link between tau and neurodegeneration was established in Cambridge, with the identification of one of the first genetic mutations in the tau gene as the cause of some familial forms of frontotemporal dementia. Furthermore, Cambridge scientists were part of the collaborative team that discovered the Huntington’s disease gene, have characterised the nature of cognitive dysfunction in Huntington’s disease and were among the first to identify specific changes in presymptomatic cases, devising a battery of tests to assess cognitive decline that is now used worldwide. Moreover, Cambridge neuropsychologists also invented a cognitive test that predicts the diagnosis of Alzheimer’s disease in patients with mild cognitive impairment. We have more than 150 researchers working in dementia research across Cambridge in a range of Departments and across all of our themes. Our research spans genetic, molecular and cellular models of neurodegeneration through to the characterisation of human pathophysiology of dementia, to early phase clinical trials.

Our success is built on the effective integration of preclinical and clinical research programmes with major specialist NHS services, and includes strategic partnerships, the UK Dementia Research Institute (brings together diverse expertise – from biological to physical sciences – to boost our understanding of the earliest stages of neurodegeneration), the MRC Laboratory of Molecular Biology (a research institute dedicated to the understanding of important biological processes at the levels of atoms, molecules, cells and organisms, providing knowledge needed to solve key problems in human health), the ALBORADA Drug Discovery Institute (couples disease knowledge and biology expertise of academic community with high quality, innovative drug discovery technologies), the NIHR Biomedical Research Centre, the Wolfson Brain Imaging Centre (a major research facility in the University of Cambridge, dedicated to bringing the latest imaging research imaging protocols to both cognitive and clinical research). Furthermore, there already exists many very successful interdisciplinary research projects in Cambridge in this area, which include, but are not limited to The NIMROD study (Neuroimaging of Inflammation in Memory and Other Disorders, an exciting and important study about the role of inflammation in dementia and related disorders), the CamCAN study (The Cambridge Centre for Ageing and Neuroscience, a large scale collaborative project that uses epidemiological, cognitive and neuroimaging data to understand how individuals can best retain cognitive abilities into old age) and the Cambridge Centre for Parkinson Plus.

A key component to the success of neurodegenerative brain research in Cambridge is the multidisciplinary nature of the academic interactions. Neurologists, neuropsychologists, neuropsychiatrists, neurosurgeons, molecular biologists, epidemiologists, geneticists, physicists, chemists, biochemists and pharmacologists all collaborate with the communal aim of understanding these diseases and identifying new treatments. You can watch a short film on this interdisciplinary approach taken by members of Cambridge Neuroscience in Catching The Memory Thief (filmed in 2016).
HISTORY
HISTORY
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David Klenerman is a physical chemist who graduated and completed his doctorate at Cambridge University working with Professor Ian Smith on infra-red chemiluminescence for his PhD in 1985. This was followed by postdoctoral research at Stanford University, California with Professor Dick Zare on high overtone chemistry. He then returned to the U.K. and worked for seven years for BP Research in their Laser Spectroscopy Group before returning to the Department of Chemistry, University of Cambridge, progressing to a Professorship. He is currently a Royal Society Glaxo Wellcome Professor of Molecular Medicine. At Cambridge, his work has focussed on the development and application of physical methods, particularly laser spectroscopy and single molecule fluorescence, to biological and biomedical problems. He is a Fellow of the Royal Society and the Academy of Medical Sciences.

Abstract: The aggregation of proteins such as αβ, tau and α-synuclein play a critical role in the development and spread of neurodegenerative disease through the brain. Although these diseases are characterised by the formation of microscopic fibrillar aggregates, a body of evidence suggests that it is the diffusible nanoscopic aggregates formed earlier in the aggregation process that cause neuronal dysfunction and ultimately cell death. To characterise these nanoscopic aggregates which are present at low concentration and in a range of sizes and structures, we have developed a single molecule approach. This allows us to measure the number, size and shape of the aggregates with 20 nm resolution in cell models, samples derived from post-mortem human brain and also cerebrospinal fluid and blood samples from live patients. The talk will firstly describe the principle of the methods used to characterise protein aggregates and summarise our work studying how the aggregates change during the development of disease. Then our work characterising protein aggregates in serum will be presented, which suggests that this is a promising approach for early diagnosis of disease.
Achieving better brain health and wellbeing in older age and early detection of memory problems

Session One: 09:25-09:50

Professor Barbara J Sahakian DSc FBA FMedSci is based at the University of Cambridge Department of Psychiatry and Behavioural and Clinical Neuroscience Institute. She specializes in various fields including psychopharmacology, neuropsychology, neuropsychiatry, neuroimaging, and neuroethics. She holds numerous prestigious positions, including Honorary Clinical Psychologist at Addenbrooke’s Hospital, Fellow of Clare Hall, Cambridge, and Fellow of the British Academy and the Academy of Medical Sciences. Her work spans cognition and motivation in brain injury, cognitive deficits in depression, and early treatment of Alzheimer’s disease. She has authored over 560 publications in prominent scientific journals and is known for her contributions to neuroscience and mental health policy. Additionally, she has been involved in important initiatives such as the UK Government Foresight Project on Mental Capital and Wellbeing and the World Economic Forum’s Future of Neurotechnologies and Brain Science. Sahakian co-invented the neuropsychological CANTAB and EMOTICOM tests (www.cambridgecognition.com) and the University of Cambridge/PEAK Advanced Training Programme and the Wizard Apprentice Memory Game (www.peak.net). Her recent work also includes research on the effects of COVID-19 on the brain, cognition, mental health, and wellbeing.

Abstract: To realise our potential throughout our life and to ensure a flourishing society, it is important to focus on good brain health and wellbeing. Environmental factors and our behaviour can improve our brains, cognition and mental health or detract from it. Our diet, our sleep and our social support systems are all key to improving brain health and cognition and reducing the risk of dementia. Early detection of memory problems in older aged adults, including amnestic mild cognitive impairment (MCI) is also important to utilize current symptomatic treatments and future treatments which are aimed at slowing or halting the underlying disease process. CANTAB Paired Associate Learning has been shown to be sensitive to the early detection of MCI and mild Alzheimer’s disease, in addition poor PAL performance is associated with increased levels of tau and beta-amyloid and reduced hippocampal volume. Cognitive training using games on iPads or mobile phones may be beneficial for improving learning and memory in patients with MCI or stroke.

Emerging therapies in dementia: a new era

Cath Mummery is a consultant neurologist at the National Hospital for Neurology and Neurosurgery. She is chair of the NIHR Dementia Translational Research Collaboration, building a national unified trials network for early phase clinical trials in dementia. She is Head of Clinical Trials at the Dementia Research Centre, Institute of Neurology, University College London, and Deputy Director for the Leonard Wolfson Experimental Neurology Centre, a cutting-edge research facility dedicated to the conduct of early phase trials in neurodegeneration. Over the past 16 years, she has been chief investigator on over 20 early phase drug trials of potential disease modifying agents in sporadic Alzheimer’s disease (AD) and genetic forms of AD and frontotemporal dementia, including immunotherapies against amyloid and tau, and novel mechanisms in first in human trials including checkpoint inhibitors, gene silencing and AAV genetic therapies.

As clinical lead for the UCL Neurogenetic Therapies Programme, she has led a programme of innovative collaboration between industry and academia, developing novel biomarkers in a trial of a genetic therapy and introducing new methods to measure real time change in protein production/clearance in a gene silencing trial. Alongside her clinical work as Head of the cognitive service at NHNN, she was until recently the deputy chair of the NHSE Neuroscience Clinical Reference Group and chair of the Association of British Neurologists Services Committee, leading neurology service development and support in the UK. She is a member of the Alzheimer’s Research UK taskforce, dedicated to raising awareness of dementia and reducing barriers to early and accurate diagnosis, and access to potential treatments.

Abstract: The route to therapies in dementia has been a long and at times tortuous road, but we are now at a pivotal moment in dementia research and treatment: the beginning of disease modification and a new way of working. In the first part of the talk, I’ll chart how progress in AD translational research has led to more sophisticated trial design and execution, and an increase in complexity and range of targets and technologies being used. I’ll summarise the converging results across anti amyloid immunotherapies, then explore the proliferation of novel methods in early phase trials, in particular genetic therapies, focussing on recent results that show promise, and how collaborative work with industry can bring experimental medicine into the trials environment and enhance understanding of trial results. In the second part of the talk, I’ll discuss the challenges in our translational research space and of implementation of these new therapies, and how our systems need a major overhaul if we are to build on the UK’s translational research reputation and avoid the tragedy of having a drug but not being able to deliver it safely and equitably to patients.


Commercial clinical trials in the UK: the Lord O’Shaughnessy review
Ben Underwood
Psychiatry

How can we improve clinical dementia care now and in the future?

Session Two:
11:00-11:25

Ben studied natural science at Oxford University and medicine in London. He completed his psychiatric training in Cambridge, including a PhD with Professor David Rubinsztein looking at autophagy up-regulating drugs as potential disease modifying agents in dementia. He is currently an Assistant Professor in applied and translational old age psychiatry at the University of Cambridge and honorary consultant psychiatrist at Cambridgeshire and Peterborough NHS Foundation Trust (CPFT). He is research and development director at CPFT, clinical lead for dementia in the East of England for the CRN, national CRN lead for stratified medicine in dementia, ARUK network co-ordinator for the East of England and co-organises the Cambridge Advance online course in translational medicine. He is clinical director of the Gnoode Goldman Sachs unit for translational neuroscience and the Windsor Unit at Fulbourn Hospital which seek to connect patients to the latest research and clinical trials.

Abstract: Dementia is one of the most pressing clinical problems of our time. It is a significant cause of morbidity, mortality and economic burden and is a problem that will continue to grow as the global population ages. In the medium term, better treatments that provide disease modification are needed. This is an exciting time as the first clinical trials describing disease modification have been reported this year, though with concerns around cost, deliverability and safety. More trials using diverse approaches are underway and new approaches to clinical trials, for example using adaptive and platform designs, allow for rapid identification of repurposed compounds. In the short term, there are further questions as to how we can optimise the current services for those living with dementia. In this talk, we will consider work in Cambridge addressing both these approaches.


Exogenous Tau affects intracellular organelle morphology and neuronal signalling

Gabriele Kaminski Schierle is Professor of Molecular Neuroscience at the University of Cambridge, UK, and serves as the leader of the Molecular Neuroscience group. Her research revolves around the application of optical techniques to investigate the fundamental molecular mechanisms underlying neurodegenerative diseases, including Alzheimer’s and Parkinson’s. Additionally, she holds the position of Director of MPhil in Biotechnology at the Department of Chemical Engineering and Biotechnology, while also being a fellow at Robinson College, Cambridge. Professor Kaminski Schierle’s current research focuses on advancing the development of transparent microelectrode arrays. These innovative arrays are designed to seamlessly integrate with high-resolution imaging methods, allowing for simultaneous analysis of neuronal function and amyloid formation. This research is particularly significant, as it sheds light on the processes occurring in neurodegenerative diseases where abnormal protein aggregates, such as amyloids, play a pivotal role. By combining cutting-edge imaging techniques with neuronal function analysis, her work contributes to a deeper understanding of these diseases at a molecular level.

Abstract: The microtubule-associated protein Tau (MAPT) is implicated in various human neurodegenerative diseases. Previous research, including our own work, has established that Tau can propagate within the central nervous system, a phenomenon closely associated with the progression of Alzheimer’s disease (AD)\textsuperscript{1,2,3}. Additionally, we have demonstrated that the uptake of monomeric Tau into cells significantly exacerbates Tau pathology\textsuperscript{3}. Here, we investigated the impact of Tau uptake on organelle morphology and on neuronal signalling. We conducted organelle morphology analyses using different model systems, including mammalian COS-7 cells, primary rat cortical neurons, and human glutamatergic neurons derived from induced pluripotent stem cells (iPSCs). To study organelle topology following Tau uptake, we employed Structured Illumination Microscopy (SIM). Electrophysiology experiments were performed in rat hippocampal neurons. Our findings reveal that Tau uptake results in the collapse of the tubular endoplasmic reticulum (ER) in both COS-7 cells and human glutamatergic neurons which has significant implications for neuronal physiology and signalling. In particular, we show that the addition of Tau alone to primary hippocampal neurons do not induce a change in the evoked excitatory postsynaptic potential response, however, optogenetically induced stimulation together with Tau leads to the inhibition of the latter. Additionally, we observe a reduction and fragmentation of microtubular structures in COS-7 cells, accompanied by the clustering of enlarged lysosomes. Interestingly, lysosomal clustering has been recently shown to occur in AD patients\textsuperscript{4}. The synchronised defects in organelle morphology and distribution suggest a potential mechanism by which Tau uptake disrupts inter-organelle communication and homeostasis. Preliminary studies indicate that blocking Tau endocytosis can restore a healthy ER phenotype, suggesting a possible therapeutic approach against tauopathy.

Authors: Alexandra Grba, Sagnik Middya, Belquis Haider, Marius Brockhoff, Ana Fernandez-Villegas, Tanja Fuchsberger, Miranda Robbins, Ernestine Hui, Meng Lu, Nino Läubli, Edward Ward, George Malliaras, Ole Paulsen, Clemens Kaminski, Gabriele Kaminski Schierle


Dr Benjamin Ryskeldi-Falcon holds a BSc in human genetics from University College London. He completed his graduate studies at the MRC Laboratory of Molecular Biology (LMB) with Dr Michel Goedert, receiving a PhD in molecular biology from the University of Cambridge in 2016. From 2016 to 2019, he carried out postdoctoral research at the LMB with Dr Michel Goedert and Dr Sjors Scheres, where he helped to determine the cryo-electron microscopy (cryo-EM) structures of assembled tau in neurodegenerative diseases. Since October 2019, Benjamin has led a research group at the LMB, with a focus on the molecular mechanisms of protein assembly in neurodegenerative disease. Benjamin is a Young Investigator at the European Molecular Biology Organisation and a Co-investigator at the UK Dementia Research Institute. For his research, Benjamin was awarded the Alzheimer’s Research UK Rising Star Award in 2019 and the Hans and Ilse Breuer Foundation Alzheimer Research Prize in 2022.

Abstract: Neurodegenerative diseases, including dementias, are characterised by the abnormal assembly of specific proteins in the brain. Mutations in the genes encoding each of these proteins give rise to assembly and inherited disease, demonstrating a causal role. However, the molecular mechanisms of protein assembly in neurodegenerative disease are largely unknown. Electron cryo-microscopy (cryo-EM) can be used to determine the structures of neurodegenerative-disease associated protein assemblies from patient brain. In this talk, I will focus on our recent work on the cryo-EM structures of assembled TAR DNA-binding protein 43 (TDP-43). The abnormal assembly of TDP-43 is the pathological hallmark of amyotrophic lateral sclerosis (ALS) and multiple types of frontotemporal lobar degeneration (FTLD), which cause different frontotemporal dementias. TDP-43 assembly is also common in other diseases, including Alzheimer’s and Parkinson’s. We found that TDP-43 assembles into amyloid filaments in these diseases. The structures establish that TDP-43 adopts distinct filament folds in different types of FTLD. Low sequence complexity leads to chemically distinct filament surfaces and confers structural variability to TDP-43 filaments. The structures also indicated a role for post-translational modifications of TDP-43 in filament formation and structural variability. This work enhances our understanding of the molecular pathogenesis of ALS and FTLD. The structures of pathological TDP-43 filaments will guide mechanistic studies into TDP-43 assembly, as well as the development of diagnostic and therapeutic strategies.


Hugh Markus is Professor of Stroke Medicine and Honorary Consultant Neurologist in the Department of Clinical Neurosciences at the University of Cambridge, UK. His undergraduate training was at the Cambridge and clinical medical training at the University of Oxford. He trained in Medicine at Oxford and Nottingham and in Neurology in London before being appointed as Senior Lecturer and then Reader in Neurology at King’s College London. He then moved to Professor of Neurology at St George’s, University of London, before moving to his current post in 2013. He spends approximately half of his time in clinical care of stroke patients, including hyperacute stroke care as well as specialist stroke interests including running a National CADASIL Clinic. His research applies genetic and imaging techniques to investigate the pathogenesis of stroke and vascular cognitive impairment to develop new treatments. He has a particular interest in small vessel disease and vascular cognitive impairment, using MRI to investigate disease mechanisms and explore why the disease causes cognitive impairment, and developing new treatment approaches. He is Editor-in-Chief of the International Journal of Stroke.

Abstract: Cerebral small vessel disease (CSVD) is not only the most common cause of vascular dementia but we now appreciate it is also a major determinant of whether neurodegenerative pathologies, such as Alzheimer’s, result in clinical dementia during life. This makes it a potential tractable treatment target with great public health potential. Recent exciting data suggest intensive treatment of vascular risk factors can reduce incidence of all dementia subtypes. Involvement of the neurovascular unit and particularly the extracellular matrix and matrisome are increasingly implicated in the pathogenesis of CSVD, with increased blood brain barrier and neuroinflammation visualized on imaging studies. These processes represent potential therapeutic targets which could have a major impact of treating dementia.


András’ research laboratory develops and uses human neural organoid models and multi-omics approaches to explore mechanisms underlying motor neurone disease, dementia and traumatic injuries and to inform novel therapeutic strategies. He obtained his degree in medicine and then carried out his PhD studies in neurosciences at the CRUK Beatson Laboratories in Scotland and the University of Cambridge. Following his postdoctoral research training in neural regeneration in Cambridge with Professor Robin Franklin, he completed basic speciality training in general medicine and higher specialist training in clinical neurology. During his clinical programme, he held a clinical lectureship in medicine and later a university fellowship in neurosciences between 2010 and 2013, which helped to kick-start his independent research group. Currently, he is heading a human neurobiology research lab at Van Geest Centre for Brain Repair in the Department of Clinical Neurosciences, and he has a clinical appointment as Honorary Consultant in Neurology at the University of Cambridge. He received the MRC Clinician Scientist Fellowship Award in 2017, the ARUK David Hague Young Investigator of the Year Award in 2022 and the MRC Senior Clinical Fellowship Award in 2023.

Abstract: We are just beginning to understand the pathomechanisms underlying fatal and untreatable neurodegenerative disorders, such as amyotrophic lateral sclerosis (ALS). Animal models and two-dimensional human stem cell-derived culture platforms provided major insights into ALS-related molecular disturbances, highlighting potential therapeutic targets. However, these models do not faithfully recapitulate the human-specific aspects of cell diversity, complex cell interactions or pathobiology, which may have hampered therapeutic advances. To help overcome these issues, we developed an ALS patient-specific three-dimensional neural organoid slice culture system, a complementary human model that mimics CNS tissue architecture and captures early pathological hallmarks. In my talk, I will provide proof-of-principle examples for using our novel platform combined with multi-omics and biological assays for precise target identification and pre-clinical drug testing.


Leo Chouliaras is an Assistant Professor and Consultant in Old Age Psychiatry. He is also a Clinical Hub Advisor at the Early Detection of Neurodegenerative Diseases (EDON) initiative. His undergraduate training was at the Aristotle University of Thessaloniki in Greece and subsequently completed his PhD at the University of Maastricht in the Netherlands. He trained in psychiatry at Oxford and Cambridge before moving to his current post in 2023. He splits his time between clinical work in a dementia and old age psychiatry service and research on the role of epigenetic mechanisms and blood biomarkers in neurodegeneration and particularly in Lewy Body Dementia.

Abstract: The epigenetic mechanism of DNA methylation has been implicated in the pathophysiology of neurodegenerative disorders such as Lewy Body Dementia (LBD). DNA methylation profiling may help to identify novel treatment targets and early disease markers. We hypothesised that DNA methylation alterations are associated with presence of disease pathology in the brain and are also detectible in blood due the influence of genetic and environmental factors as well as immune system changes associated with LBD.

Genome-wide DNA methylation profiling was carried out using whole genome bisulphite sequencing in post-mortem brain tissues of patients with LBD and in controls. Using laser-capture microdissection DNA was isolated from neurons bearing Lewy Body pathology and was compared to DNA from to neurons without pathology. In parallel, reduced representation bisulfite sequencing was carried out in blood samples from LBD patients and controls. DNA methylation alterations at specific CpG sites as well as at promoter, CpG island and CpG shore regions were compared between LBD cases and controls.

The results suggest that DNA methylation alterations are prevalent in brain and blood in LBD and suggest that profiling DNA methylation in dementia shows promise both for the identification of novel specific gene targets and for explorations as a peripheral biomarker.
Mina Ryten is Professor of Clinical Genetics at UCL Great Ormond Street Institute of Child Health and is an Honorary Consultant in Clinical Genetics at Great Ormond Street Hospital for Children and at Guy’s Hospital. She is a clinician scientist with experience in both clinical and research settings. In her clinical practice she cares for individuals and families with, or at risk of, a range of conditions which may have a genetic basis. As well as providing a diagnosis, the aim of her clinics is to help individuals affected by a genetic disorder live as normally as possible with their condition. Mina’s research lab focuses on the use of transcriptomics, primarily derived from human brain, to improve the molecular understanding of complex and rare neurological disorders.

UK Dementia Research Institute at Cambridge

Leadership: Mina Ryten (from January 2024)
David Rubinsztein (Interim Director)

Website: https://ukdri.ac.uk/centres/cambridge

Launched in 2017, the UK Dementia Research Institute (UK DRI) is the single biggest investment the UK has ever made in dementia thanks to founding funders the Medical Research Council (MRC), Alzheimer’s Society and Alzheimer’s Research UK. The UK DRI breaks new ground by bringing together world-leading expertise in biomedical, care and translational dementia research in a national institute currently made up of over 750 researchers and a support team of over 50, all growing rapidly.

The Institute carries out research relevant to all dementias, including Alzheimer’s disease, Parkinson’s disease, frontotemporal dementia, vascular dementia, Huntington’s disease and beyond. The hub is based at UCL, with Centres hosted at: University of Cambridge, Cardiff University, University of Edinburgh, Imperial College London and King’s College London. The Care Research & Technology Centre based at Imperial College London and the University of Surrey joined in 2019.

Scientists at the UK DRI at Cambridge are using cutting-edge approaches to build our understanding of the biological processes behind the earliest stages of neurodegeneration and ageing. For instance, they are exploring mechanisms causing the loss of vital connections between neurons and the pathways that drive repair of these connections - essential for memory formation and survival of brain cells. They are also studying the causes and effects of build-up and spread of misfolded proteins in disease. They have already identified a number of promising targets for testing in patients and hope to identify new key molecular targets that can be translated into effective new treatments that can stop, slow down or reverse dementia.

The Clifford Allbutt Building on the Cambridge Biomedical Campus where the UK Dementia Research Institute and the ALBORADA Drug Discovery Institute are located
John Skidmore is a chemist by training, receiving a BA and DPhil from the University of Oxford. Following a post doc at the University of Liverpool with Professor Stan Roberts, John joined GSK where he worked as a medicinal chemist and project leader in the pain and neurodegeneration therapeutic areas. In 2010 John moved to the University of Cambridge, where, funded through the Wellcome Trust’s Seeding Drug Discovery scheme, he led a number of protein-protein interaction inhibitor projects. In 2015 John moved within the University, to his present position as the CSO of the Alzheimer’s Research UK Cambridge Drug Discovery Institute. To discuss possible targets, you can contact John at js930@cam.ac.uk

The ALBORADA Drug Discovery Institute

Leadership: Chief Scientific Officer - John Skidmore
Lead Academic Scientist - Roger Barker

Website: https://cambridge-ddi.alzheimersresearchuk.org/

The ALBORADA Drug Discovery Institute (ADDI) at Cambridge bridges the gap between the deep disease understanding of academia and the drug development capabilities within the pharmaceutical/biotechnology industry and clinical centres of excellence. The ADDI is one of three Institutes within the Alzheimer’s Research UK Drug Discovery Alliance, working alongside Institutes at the University of Oxford and University College London. The Alliance is accelerating the discovery of novel, effective therapeutics for Alzheimer’s disease and other neurodegenerative diseases. Housed in the heart of the Cambridge Biomedical Campus, the ADDI aims to build collaborative projects across the University and beyond. The Institute is made up of dedicated drug discovery teams led by a Chief Scientific Officer, Dr John Skidmore and a Lead Academic Scientist, Professor Roger Barker.
James Rowe
Neurodegenerative diseases and dementia theme lead

Bitesize overview of
NIHR Cambridge Biomedical Research Centre

James is a Professor of Cognitive Neurology at the University of Cambridge. He studies the mechanisms and treatment of neurodegenerative disorders, including frontotemporal dementia, Progressive Supranuclear Palsy and Alzheimer’s disease. He trained in medical sciences and experimental psychology at Cambridge, before clinical medicine at Oxford and a PhD at UCL. After specialist training in London and Copenhagen, he returned to Cambridge where he now directs the Centre for Frontotemporal Dementia, including its regional specialty clinics, and leads the Clinical program in the Centre for Parkinson-plus. He is Associate Director of Dementias Platform UK, and Chief Scientific Adviser to Alzheimer’s Research UK. James’ expertise in experimental medicine brings together multimodal brain imaging, genetics, psychopharmacology and computational models to transform the mechanistic understanding of human disease into new treatments and clinical trials.

Cambridge Biomedical Research Centre
Neurodegenerative Disease and Dementia Theme

Leadership: James Rowe and Caroline Williams-Gray

Website: https://cambridgebrc.nihr.ac.uk/research/neurodegenerative-disease-and-dementias

The NIHR Cambridge BRC is part of the NIHR and hosted by Cambridge University Hospitals NHS Foundation Trust in partnership with the University of Cambridge, and includes a major commitment to neurodegenerative disease and dementia research. We bring together the expertise and resources of both partners to support ‘translational research’, turning scientific discoveries into new ways to detect, treat and prevent disease.

We work closely with other NIHR BRC’s and NHS organisations in the Dementia Translational Research Collaboration (DTRC), together with universities, research councils, research charities, industry and of course patients and the public. Our Academic, Healthcare and Industry partnerships create a vibrant environment to train and mentor the next generation of research leaders and to work with patients, communities and the public to understand their research needs and priorities.

The Neurodegenerative Disease and Dementia theme of the BRC works especially closely with the BRC themes for Mental Health, Imaging, Advanced Therapies, Nutrition obesity and metabolism, the Cambridge Brain Bank and CPFT. Our research teams are building research capacity and maximizing impact through experimental medicine studies and clinical trials that promote inclusion of under-served groups. For Alzheimer’s disease, Parkinson’s disease, Lewy Body Dementia, Vascular Dementia, Huntington’s disease, Frontotemporal dementias and Progressive Supranuclear Palsy we are:

1. Developing new tests for early detection of neurodegenerative disease,
2. Validating new treatment targets and accelerating clinical trials
3. Improving the research infrastructure for research and training
4. Preventing dementia in the context of co-existing diseases and frailty
5. Seeking to treat early and in those most at risk

The NIHR Cambridge Biomedical Research Centre is based on the Cambridge Biomedical Campus.
Shalom (Shaz) Henderson is a PhD candidate, Gates Cambridge scholar, and speech-language pathologist. Her studies span the MRC Cognition and Brain Sciences Unit, the Department of Clinical Neurosciences, University of Cambridge and the Cambridge Centre for Frontotemporal Dementia and Related Disorders. Her research focuses on understanding how word meaning is stored and accessed in the brain, and the nature of impairments that result when crucial brain regions are affected by Primary Progressive Aphasia. Her work also includes novel aphasia research tools designed to be simple, scalable, sensitive, yet speak to the neurobiology of language. As a clinician-researcher, she has been working primarily with patients diagnosed with FTLD and related disorders for the past 6 years and is passionate about translating research findings to the clinical context.

**Abstract:** Language is commonly affected in many dementias as a dominant or adjunctive symptom. Speech and language deficits are the primary symptom in primary progressive aphasia (PPA), associated with frontotemporal lobar degeneration and Alzheimer’s disease. Deficits are also frequently found in Parkinson’s disease, progressive supranuclear palsy and corticobasal syndrome. Progressive language deterioration negatively affects individuals’ quality of life, carer burden, and outcome. Enabling early and accurate diagnosis is a priority for inclusion in clinical trials and targeted speech-language interventions. I will discuss barriers to the assessment of progressive aphasias and present three exemplars of transdiagnostic approaches to improve timely and accurate diagnosis and characterization of language-based dementias.


Dr. Maura Malpetti is the Race Against Dementia Alzheimer’s Research UK Fellow at the University of Cambridge’s Department of Clinical Neurosciences. She earned her BSc and MSc degrees at Milan’s Vita-Salute San Raffaele University, specializing in nuclear medicine and FDG PET research in Alzheimer’s disease and frontotemporal dementia. Later, she pursued her PhD in Clinical Neurosciences at the University of Cambridge, focusing on in vivo neuroimaging markers, longitudinal modeling in tauopathies, and training as a visiting researcher at the University of California San Francisco (UCSF) Memory and Aging Center and the Ludwig Maximilian University of Munich. Dr. Malpetti’s research primarily centers on using neuroimaging techniques (multi-tracer PET and MRI) to investigate neurodegenerative diseases’ pathophysiology. Her goal is to identify early diagnostic and prognostic markers in dementia, aiding in preclinical model validation and informing new disease-modifying treatment strategies. Her particular focus lies in researching clinically viable PET and other biomarkers for inflammation and synaptic loss in frontotemporal lobar degeneration and related neurodegenerative disorders. Her research program integrates imaging and clinical data with fluid markers and post-mortem pathology, striving to reveal common cross-diagnostic themes and mechanisms.

Abstract: Preclinical, genetic and imaging studies indicate brain inflammation as an important pathogenic mechanism in in Alzheimer’s disease, frontotemporal dementia, and related disorders. However, immunotherapeutic strategies are hampered by lack of knowledge about individual differences in inflammation, their causes and consequences. Using PET imaging we can now localise and quantify in vivo brain inflammation in people with these conditions. Using positron emission tomography (PET) with a tracer binding to TSPO (overexpressed in activated microglia), we recently showed that higher regional inflammation correlates with clinical severity and importantly predicts faster clinical decline in people with Alzheimer’s disease (Malpetti et al., 2020), frontotemporal dementia (Malpetti et al., 2023), and progressive supranuclear palsy (PSP; Malpetti et al., 2021). This strongly supports the role of central nervous system inflammation in accelerating disease progression in people with dementia. In people with these conditions, a range of anti-inflammatory treatments could be helpful to slow or prevent decline. My group is now investigating diverse methods to measure inflammation with clinically relevant and mechanistically informative blood markers in people with dementia, capturing the immune cells involved and the chemical signalling patterns between them. Establishing inflammatory “fingerprints” from blood in people with dementia will facilitate accessible and scalable biomarkers to support personalised medicine, early screening strategies, and target-specific immunomodulatory therapies.


AI for better brain health - turning the hype into reality in dementia

Timothy Rittman is a Senior Clinical Research Associate at the University of Cambridge where he studies rare types of dementia, combining neuroimaging, cognitive assessments and neuropathology to understand how these diseases affect the whole brain. He also has an interest in translating methods from artificial intelligence and big data for use in memory clinics. Tim co-leads the DEMON dementia network’s Imaging Working group and is an adviser to the World Young Leaders in Dementia. He is an Honorary Consultant Neurologist at Addenbrookes hospital, as a consultant in the Addenbrookes Memory Clinic, and leading a clinic for people with Progressive Supranuclear Palsy and Corticobasal Degeneration, and co-leading a dementia genetics clinic.

Zoe Kourtzi is Professor of Computational Cognitive Neuroscience at the University of Cambridge. Her research aims to develop predictive AI-guided models of neurodegenerative disease and mental health with translational impact in early diagnosis and personalised interventions. Kourtzi received her PhD from Rutgers University and was postdoctoral fellow at MIT and Harvard. She was a Senior Research Scientist at the Max Planck Institute for Biological Cybernetics and then a Chair in Brain Imaging at the University of Birmingham, before moving to the University of Cambridge in 2013. She is a Royal Society Industry Fellow, Fellow and Cambridge University Lead at the Alan Turing Institute, and the Scientific Director for Alzheimer’s Research UK Initiative on Early Detection of Neurodegenerative Diseases (EDoN).

Abstract: Dementia is a growing global challenge. Alzheimer’s disease (AD) is the commonest type of dementia, and is characterised by progression from normal cognition, to mild cognitive impairment (MCI), to dementia. However, not all individuals with MCI develop dementia. Predicting whether individuals with MCI or older people without symptoms will decline or remain stable is impeded by patient heterogeneity due to factors such as comorbidities, lifestyle and disease severity. Despite the importance of early diagnosis of AD for prognosis and personalised interventions, we still lack robust tools for predicting individual progression to dementia. Here, we propose a novel AI-guided trajectory modelling approach that mines multimodal data to derive individualised prognostic scores of cognitive decline due to AD, effective both for MCI and before symptoms occur. Our approach has the strong potential to facilitate effective stratification of individuals based on prognostic disease trajectories, reducing patient misclassification with important implications for clinical practice and discovery of personalised interventions.

Alzheimer’s disease causes changes detectable on structural MRI neuroimaging that can be identified using artificial intelligence approaches to aid earlier diagnosis and better prognostication.


Can we realistically repair the brain in Parkinson’s?

Roger Barker is the Professor of Clinical Neuroscience at the University of Cambridge and Consultant Neurologist at Addenbrooke’s Hospital. He is a member of the John van Geest Centre for Brain Repair, Department of Clinical Neurosciences and Wellcome-MRC Cambridge Stem Cell Institute. He runs the regional NHS Huntington’s Disease (HD) as well as clinics in Parkinson’s Disease (PD). His research investigates the heterogeneity of these disorders and its basis which has informed work he has done on trialing new experimental therapeutics for these conditions including cell and gene therapies as well as drug repurposing. He is lead academic scientist of the ARUK funded Drug Discovery Institute in Cambridge as well as the John Van Geest Centre for Brain Repair. He is Co-editor in chief of the Journal of Neurology.

Abstract: Parkinson’s disease (PD) is a common neurodegenerative disorder that is characterised by the loss of nigrostriatal dopaminergic neurons and their projection into the putamen. However, while the pathology is not restricted to this site, its critical role in the clinical features of PD is seen through the beneficial effects of dopaminergic therapies in people with Parkinson’s, especially in the early stages of the condition. Nevertheless, these therapies create their own side effects including neuropsychiatric problems, exacerbation of autonomic problems as well as in the long term L-dopa induced dyskinesias which can be severely debilitating in some patients. As such, there is a need for a better therapy targeting this aspect of the pathology in PD and this includes repairing this dopaminergic network using cell replacement therapies. This reparative approach has involved a number of different sources of dopamine cells including those from the developing human fetal brain as well as more recently from human stem cell derived cell lines. Overall, trials using human fetal tissue have shown proof of concept with the best patients have surviving grafted dopamine cells decades after implantation with restorative of putamenal dopamine levels to normal and clinical benefits leading to some patients stopping their oral dopamine medication. However, the results have been inconsistent with some patients developing side effects such as graft induced dyskinesias and in addition the alpha synuclein pathology of Parkinson’s has been seen to emerge in the grafted dopaminergic neurons over time. This has led to a re-evaluation of the approach, and with this the development of new stem cell derived dopamine therapies which are now entering first in human clinical trials. The results of these trials are eagerly awaited.


New genetic therapies for Huntington’s disease – Challenges and opportunities

Sarah Tabrizi
University College London

Abstract: Huntington’s disease is the world’s most common genetic dementia and a devastating neurodegenerative disorder for which we have no approved disease-modifying treatments. The molecular pathogenesis of Huntington’s disease is complex, with toxicity arising from full length expanded Huntingtin and N-terminal fragments prone to misfolding due to proteolysis or aberrant intron-1 splicing, and somatic expansion of the CAG repeat in the HTT gene driving disease. My talk will focus on the current “state of the field” for Huntington’s disease genetic therapies targeting huntingtin DNA and RNA, including the early dosing termination of the Roche Phase 3 antisense oligonucleotide trial, and a new biological staging system to allow trials much earlier in the disease course. It is timely to reflect on lessons learned, where the field stands now, and our challenges and opportunities for the future.


Meet the Poster judges

Head Judge
David Bulmer, Pharmacology
Inflammatory bowel disease
Irritable bowel syndrome
Pain

Edward Azezov, DRI, Cambridge
Alzheimer’s disease & Dementia
Endoplasmic Reticulum
Protein folding and aggregation

Caroline Williams-Gray,
Clinical Neurosciences
Parkinson’s disease
Immune system
Neuroinflammation

Janin Lautenschlaeger,
Cambridge Institute for Medical Research
Alzheimer’s disease
Amyotrophic lateral sclerosis (ALS)
Parkinson’s disease

Kate Baker,
MRC Cognition and Brain Sciences Unit
Cognitive impairment
Genetic disorders
Language disorders

John Apergis-Schoute,
Queen Mary University of London
Neural circuits
Emotion
Appetite

Annemiek Apergis-Schoute,
Queen Mary University of London
Obsessive Compulsive Disorder
Psychiatric disorders
Human Imaging

Craig Brierley,
Office of External Affairs and Communications
Press releases
Science writing
Media
Neurons, Circuits and Networks (NCN) unites researchers working with radically different datasets and at distinct scales of investigation – from cellular signalling networks, to neuronal circuits, to large-scale networks of interacting brain regions. There are many research groups in Cambridge whose work is revolutionising our understanding of Neurons, Circuits and Networks across all scales.

This theme focuses on the structure and function of individual neurons, as well as their organisation into circuits and larger-scale networks of neuronal populations. We aim to understand how neuronal circuits give rise to complex behaviours and cognitive processes both in health and in disease. Ultimately, we believe that a mechanistic understanding of circuit function and dysfunction will help drive innovation both in treatments of brain disease and in biologically inspired artificial intelligence.

A major strength of the Neurons, Circuits and Networks community in Cambridge is that it isn’t siloed, either by scale of investigation – from molecules to whole brains – or by conventional divisions between departments. Instead, we bring together a broad range of researchers from Cambridge-based institutes such as the MRC Laboratory of Molecular Biology and the Wellcome Sanger Institute, as well as many different University departments including Genetics, MRC Cognition and Brain Sciences Unit, Pharmacology, Physiology, Development and Neuroscience, Zoology, Medicine, Clinical Neurosciences, Psychiatry, Psychology, Engineering and Applied Mathematics & Theoretical Physics.

Together we investigate questions such as (i) the molecular mechanisms underpinning the function of individual neurons and synapses, (ii) communication between neurons, glia and other cell types, (iii) computational and algorithmic aspects of how neurons represent and manipulate information, (iv) mechanisms of neural network development, degeneration and regeneration – from axon guidance to plasticity, (v) the neuronal circuits underpinning physiological processes such as circadian rhythms or modulation of fertility hormones, and (vi) the neuronal and network mechanisms underpinning cognitive processes – from vision and navigation to attention, learning, decision-making and reward processing. Many research groups within the theme also focus on how neural circuits and networks differ in health and disease, and how neuronal function can be manipulated for therapeutic benefit. This includes applications to understanding and better treating chronic pain, addiction, obesity, dementias, mood disorders, and other neuropsychiatric disorders such as schizophrenia.
The **Adaptive Brain Computations (ABC)** theme brings together a diverse group of scientists from across the University with shared interests in decoding how the brain senses, accumulates, maps, and combines present and past information to enable organisms adaptively to operate in their environments. This is a cross cutting theme with relevance for how the brain represents and computes information at different stages of development, instantiates social cognition, and in coordinating reflexive and higher-order behaviours, all of which depend fundamentally on neural circuits and networks, including neuronal-glial interactions. Moreover, elucidating how the brain captures and integrates information is imperative as a starting point to gain a richer mechanistic understanding of the biological and environmental pressures that extend the brain beyond its normal operating limits, ultimately to cause the outward expression of brain disorders such as autism spectrum disorder, schizophrenia, depression, ADHD, OCD, and addiction.

Research in this theme aims to elucidate the brain mechanisms that mediate neuronal plasticity and adaptive behaviour across species and scales. It works towards building a mechanistic understanding of how the brain senses, accumulates, maps, and combines present and past information about the external and internal environments, and uses them for decision-making, learning, and memory. It seeks to characterise the processes giving rise to flexible responses that adapt to changing environments and shifting goals, while maintaining operational stability and overall homeostasis. It also wishes to understand the principles and mechanisms by which evolution moulds brain circuits adaptively to distinct ecological niches and behavioural needs.

Adaptive Brain Computation researchers belong to more than 10 different department and institutes, including the Departments of Psychology, Psychiatry, Engineering, Physiology, Development and Neuroscience, Medicine, the MRC Laboratory of Molecular Biology and the MRC Cognition and Brain Sciences Unit. We work on theory and computation as well as experimental approaches, and aim to cover the full range of scales in neuroscience, from molecules to neurons and networks, to systems, to whole organism and behaviour.

Work in this theme strongly integrates with the “Neurons, Circuits and Networks” and “Brain and Machines” themes, creating further strong synergies between the Schools of Biological Sciences, Clinical Medicine, Physical Sciences, and Technology.
Research into *Lifelong Brain Development & Brain Ageing* incorporates development from before birth to old age. The lifelong brain development community in Cambridge is made up of a diverse group of researchers working in a range of disciplines spanning the Departments of Biochemistry, Clinical Neurosciences, Chemistry, Chemical Engineering and Biotechnology, Genetics, Physiology, Development & Neuroscience, Paediatrics, Psychology, Psychiatry, Education and Zoology, as well as the Gurdon Institute of Developmental Biology, the MRC Cognition and Brain Sciences Unit, the Wellcome-MRC Cambridge Stem Cell Institute and the MRC Laboratory of Molecular Biology.

Teams of researchers working within and across departments and disciplines are investigating the development of the nervous system across the lifespan at a variety of levels and using a range of model systems, including embryos of different animal species (both vertebrate and invertebrate) and human cerebral organoids (‘mini -brains’). Questions currently being investigated range from how individual neurons form and arrange themselves into a nervous system, to how brain, behaviour and cognition develop across the lifespan, from prenatal through childhood and adolescence to old age. Research at Cambridge is also focused on brain mechanisms and cognitive development in developmental conditions such as autism and ADHD, in mental health problems such as depression, anxiety and psychosis, and in degenerative conditions such as dementia and Parkinson’s Disease. Cambridge leads research on brain ageing and dementia, which is the focus of CNS2023 and is discussed elsewhere in this programme.

We link closely to key partner NHS Trusts (Cambridge University Hospitals Trust and Cambridgeshire and Peterborough NHS Foundation Trust), the UK Dementia Research Institute, and Dementias Platform UK, and national NIHR infrastructure including the Clinical Research Network (CRN) and Join Dementia Research (JDR). Within the NIHR Cambridge Biomedical Research Centre our focus is on early stage translational studies, including novel repurposing studies and cell therapies.
Social behaviour and communication are key to interactions between individuals and within groups. Interpersonal transmission of information builds relationships and sustains communities. Conversely, breakdowns in communication and social cohesion can precipitate harm and suffering for individuals and societies, with particularly powerful impacts on mental health. This theme seeks to forge cross-disciplinary research that will increase our fundamental understanding of these vital human interactions, and translate this understanding to benefit diverse individuals and groups.

Cambridge researchers allied to the Social Brain theme use a variety of techniques, including multi-method neuroimaging approaches and computational modelling, and study unique cohorts that face challenges to social behaviour and communication. This theme seeks to understand a range of cognitive processes contributing to language learning, decision making, kinship and group dynamics. Studies span the entire lifespan from development in early infancy to decline in healthy ageing or dementia; this work also encompass cross-species approaches and artificial intelligence methods that simulate, or support human communicative abilities. There are diverse opportunities for application of this research in medical, educational, technological and cultural spheres being actively developed in Cambridge.

Researchers contributing to this theme are widely distributed across the schools and departments of the University including Departments of Psychology; Zoology; Physiology, Development and Neuroscience; Psychiatry; MRC Cognition and Brain Sciences Unit; Clinical Neurosciences; Computer Science and Technology; Theoretical and Applied Linguistics; Engineering; and the Faculty of Education. This research theme is closely linked with the Cambridge Language Sciences Initiative: an Interdisciplinary Research Centre, which connects language researchers from these and other departments.
Why Brains and Machines? A brain is an organ, it has a purpose. And it’s constrained by the laws of physics, the laws of probability – the laws of the known universe. It needs to fit within these laws to perform its function. So, it is subject to the same kinds of trade-offs, constraints and costs that ‘machines’ in the engineering sense are subject.

It is now possible to measure and manipulate signals in the brain at single-cell resolution, over extended periods and with minimal unwanted impact on nervous system function. This has resulted in tremendous progress in neuroscience in the last decade and a flurry of new research technologies, clinical interventions and diagnostic tools. At the same time, this progress has resulted in a number of era-defining challenges:

• analysing, interpreting and managing a deluge of new data
• designing biocompatible sensors, hardware and algorithms to interface with living nervous systems
• developing theoretical principles for understanding how brains process information
• anticipating societal challenges and disruption due to increased human-brain-machine interaction

Conversely, many of the recent advances in information engineering and automation, particularly AI and Machine Learning, have been heavily inspired by neural architectures. This suggests an approach that marries traditional engineering disciplines with all domains of neuroscience. The Brains and Machines theme thus aims to exploit progress in neurally-inspired engineering and data science with major open challenges in neuroscience, biotechnology and biomedicine. This provides opportunities that move far beyond the traditional basic/translational divide in neuroscience to address emerging societal challenges that will define this century and the next.

Brains and Machines encapsulates the development of artificial intelligence approaches with applications in neuroscience and mental health, including computational neuroscience approaches and artificial networks to advance: a) our understanding of the workings of the brain, b) the design of neuro-inspired artificial systems, c) diagnosis of disease and prediction of treatment outcomes, paving the way to a personalised approach to mental health and brain disorder.
Neuroscience in the 21st Century is expanding beyond the traditional focus on the nervous system to consider how it interacts with the rest of the body and the role of non-neuronal cells in neurological diseases. Research in the Beyond the Neuron (BTN) theme seeks to understand the role of glia and immune cells in health and disease, particularly: (a) astrocyte, oligodendrocyte and microglia biology; (b) glia-neuronal interactions; (c) role of glia in neuroinflammation; and (d) characteristics of human immune cells in neuropsychiatric brain disorders. The theme also covers brain control of energy homeostasis. At Cambridge researchers take advantage of expertise in glial and stem cell biology to develop human models for studying the interactions between different cell types within the nervous system and identifying potential avenues for new interventions for disease. Ultimately, our aim is to translate fundamental discoveries to therapies for people with disease and in several areas that has already been achieved; for instance, we have shown that repurposing a cancer drug, which is an agonist of the retinoid X receptor, promotes remyelination in people with multiple sclerosis. This research community is highly collaborative across the Departments of Clinical Neurosciences, Physiology, Development and Neuroscience, Biochemistry, Medicine, Pharmacology, Engineering, Paediatrics and Wellcome-MRC Institute of Metabolic Sciences with close interactions with the Wellcome-MRC Cambridge Stem Cell Institute, MRC Laboratory of Molecular Biology, European Bioinformatics Institute and Sanger Institute.
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7. A novel concurrent TMS-fMRI setup for high resolution whole brain imaging: pilot data
Presenting author: Dr Moataz Assem (moataz.assem@mrc-cbu.cam.ac.uk)
Authors: Assem M 1, Woolgar A 1
Authors’ affiliations: MRC Cognition and Brain Sciences Unit

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13. Objective measures of gut dysfunction in Parkinson’s Disease
Presenting author: Ms Marta Camacho (msc72@cam.ac.uk)
Authors: Camacho M, Williams-Gray CH
Authors’ affiliations: Department Clinical Neurosciences, University of Cambridge

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17. Inflammation and Neuropsychiatric Symptoms in Frontotemporal dementia and related disorders
Presenting author: Miss Tanatswa A Chikaura (tac64@cam.ac.uk)
Authors: Chikaura TA 1, Swann P 2, O’Brien J 2, Rowe JB 1 3, Malpetti M 1
Authors’ affiliations: 1 Department of Clinical Neurosciences, University of Cambridge, University of Cambridge, 2 Department of Psychiatry, University of Cambridge, 3 MRC Cognition and Brain Sciences Unit, University of Cambridge

@tana_chikaura

16. First Steps in Using Topographic Deep Artificial Neural Network Models to Generate Hypotheses about Not-yet-detected Functional Neural Clusters in the Ventral Stream
Presenting author: Dr Kamila Jozwik (jozwik.kamila@gmail.com)
Authors: Jozwik KM 1-3, Lee H 2, Kanwisher N 2,3, DiCarlo JJ 2-4
Authors’ affiliations: 1 Department of Psychology, University of Cambridge, 2 McGovern Institute for Brain Research, Massachusetts Institute of Technology, 3 Center for Brains, Minds, and Machines, Massachusetts Institute of Technology, 4 MIT Quest for Intelligence, Massachusetts Institute of Technology

@KamilJozwik

29. Intranasal delivery of siRNA targeting ApoE4 as potential treatment of Alzheimer’s disease
Presenting author: Mr Huan Li (alyhl28@nottingham.ac.uk)
Authors: Li H 1, Alexander C 1, Harvey P 2, Zhu Z* 1
Authors’ affiliations: 1 School of Pharmacy, University of Nottingham, 2 School of Chemistry/Medicine, University of Nottingham

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40. Predicting outcomes for patients with dementia needing psychiatric inpatient care

Presenting author: Ms Oriane E Marguet (oem27@cam.ac.uk)
Authors: Marguet OE, Underwood BR
Authors’ affiliations: Department Psychiatry, University of Cambridge

42. Exploring the expression of candidate MS progression genes in human pluripotent stem cell-derived neural models

Presenting author: Ms Mollie O McKeon (mom25@cam.ac.uk)
Authors: McKeon M 1, Ban M 1, Al-Najjar R 1, Else J 1, Jacobs B 1 2, Gibbons G 1, Varga B 3, Káradóttir RT 3, Lakatos A 1 3, Sawcer S 1
Authors’ affiliations: 1 Department Clinical Neurosciences, University of Cambridge 2 Preventive Neurology Unit, Wolfson Institute of Population Health, Queen Mary University of London, London, 3 Wellcome-MRC Cambridge Stem Cell Institute, University of Cambridge

@MollieMcKeon

46. Digging deeper into pain

Presenting author: Dr Luke A Pattison (lap48@cam.ac.uk)
Authors: Pattison LA, Cloake AM, Chakrabarti S, Hilton H, Rickman RH, Higham JP, Meng MY, Paine LW, Qui L, Riffoux A, Bulmer DC, Callejo G and Smith ES
Authors’ affiliations: Department Pharmacology, University of Cambridge

@interlukein

52. Circadian clocks in human cerebral organoids

Presenting author: Dr Nina Rzechorzhek (ninar@mrc-lmb.cam.ac.uk)
Authors: Rzechorzek NM 1, Sutcliffe MA 1, Mihut A 1, Beale AD 1, Sanchez D L-D 1, Karam N 2, Baranes K 3, Peak-Chew S-Y 1, Seinkmane E 1, Karim K 3, Kotter M 3, Proctor C 2, Lancaster M 1, O’Neill JS 1
Authors’ affiliations: 1 MRC Laboratory of Molecular Biology, Cambridge, 2 Department of Engineering, University of Cambridge, 3 Department of Clinical Neurosciences and Wellcome Trust-MRC Stem Cell Institute, University of Cambridge

@Neurocool

55. Neuroinflammation is elevated in people with Parkinson’s disease with higher risk of developing dementia: baseline findings from the NET-PDD study

Presenting author: Dr Lennart R B Spindler (lrb2@cam.ac.uk)
Authors: Spindler LRB 1, Kouli A 1, Malpetti M 1, Fryer TD 1 2, Hong YT 1 2, Aigbirhio FI 1 2, White SR 3, Camacho M 1, Williams-Gray CH 1
Authors’ affiliations: 1 Department of Clinical Neurosciences, University of Cambridge, 2 Wolfson Brain Imaging Centre, University of Cambridge, 3 Medical Research Council Biostatistics Unit, Cambridge Institute of Public Health, Cambridge, 4 Department of Psychiatry, University of Cambridge

@LennartSpindler
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1. Brain organoid-based analysis of the chromatin remodeler CHD2 in human cortex development

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Keywords: Affective Disorders, Neuropsychiatry - Autism, Neuroregeneration, Chromatin remodeler, CHD2, Epigenetic modification, cortical development, neurogenesis, brain organoids, cortical spheroids.

Chromodomain helicase DNA binding protein 2 (CHD2) exhibits an essential role in cortical development, and its mutations are correlated with a variable spectrum of neurodevelopmental disorders including epilepsy and autism. Although a large number of coding mutations have been mapped in the CHD2 locus, the mechanism by which it contributes to normal and pathological corticogenesis remains unclear. In this sense, the mice model does not fully recapitulate the pathological phenotype described in human patients and thus falls short of investigating CHD2 functions in human cortex development. Additionally, in silico data predict the presence of different human-specific CHD2 isoforms, whose functions have never been addressed. To address these questions, we first characterized CHD2 expression in human cortical precursors using iPSCs-derived cortical organoids and analyzed whether its predicted isoforms are transcribed. Additionally, we engineered CHD2 mutant iPSC lines disrupting all CHD2 isoforms and investigated the effects of CHD2 depletion on the different populations of cortical neural precursors. We demonstrated that different CHD2 isoforms are expressed during human corticogenesis and that the relative proportion of these varies during this process. Finally, our data suggest that CHD2 depletion alters the cortical neurogenic process by affecting the proliferation and differentiation of cortical neural precursors. Thus, this work provides new insights into the expression and functions of CHD2 in cortical development.

2. Concept for Sleep Study using NIRS in Dementia

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Keywords: Neurocognition, Neurodegenerative Disorders, Dementia, Sleep, Near-infrared Spectroscopy, Glymphatic

Sleep is vital for wellbeing, especially when it comes to maintaining healthy brain function. One of the functions of sleep is to accelerate the clearance of metabolites in the brain from perivascular and interstitial space by employing the glymphatic system. This system is known to be most active during deep, non-rapid eye movement (NREM) sleep. Some preliminary studies in animal models indicate an impaired glymphatic clearance during sleep in Alzheimer’s and Parkinson’s disease (Buccellato et al., 2022). An understanding of the relationship between sleep, dementia and glymphatic clearance could provide an insight into dementia prognosis and help with symptom management. Unfortunately, that would require large-cohort sleep studies continuously monitoring in naturalistic settings (preferably at-home) which current glymphatic assessment systems such as PET and MRI do not provide. We propose to use multi-wavelength light-based systems to estimate changes in cerebrospinal fluid (CSF) which could indicate glymphatic variations. Broadband Near-infrared Spectroscopy (bNIRS) is one such system that can continuously monitor brain-function at the subject bedside, non-invasively. We plan to build a custom system, control optical phantoms and bedside experimental setup to first gauge the possibility of measuring CSF volume changes during sleep with bNIRS and its relationship to sleep and glymphatic flow. Finally, the aim is to translate this work in a dementia cohort and assess its viability is disease diagnosis and management.

3. VAMP2 regulates phase separation of alpha-synuclein

Presenting author: Dr Aishwarya Agarwal (aa2421@cam.ac.uk)
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Keywords: Neurodegenerative Disorders, Neuroregeneration, SNARE protein, VAMP2, Liquid-liquid phase separation, Alpha-synuclein, Lipids

Alpha-synuclein (aSYN) is an intrinsically disordered protein present predominantly in presynaptic nerve terminals...
where its physiological role involves maintenance, clustering, and recycling of the synaptic vesicle (SV) pool. A recent discovery has unveiled a new facet of aSYN behaviour - the phenomenon of liquid-liquid phase separation (LLPS). We now demonstrate that aSYN phase separation is induced, in vitro and in cells, via interaction with the vesicle-associated membrane protein 2 (VAMP2), which is a vesicular SNARE protein. Electrostatic interactions between the negatively charged C-terminal domain of aSYN and the positively charged juxtamembrane domain of VAMP2 promote this phase behaviour. Furthermore, our studies hint towards the importance of lipid membranes in regulating aSYN phase separation, since the disease-associated A30P variant of aSYN, which has decreased lipid binding fails to undergo condensate formation when co-expressed with VAMP2. Our results delineate a molecular mechanism for the regulation of aSYN phase separation, indicating a potential switch from the dispersed to the phase-separated state during vesicle cycling.

4. The potential of phytochemicals as treatments for Alzheimer’s disease

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Keywords: Neurodegenerative Disorders, Phytochemicals, Alzheimer’s disease (AD), cholinesterase inhibitors, antioxidant

Approximately 50 million people globally suffer from dementia and for which Alzheimer’s disease (AD) represents the majority of dementia cases. A reduction in acetylcholine (ACh) signalling is the premise for the adoption of cholinesterase inhibitors (ChIs) as the first-line pharmacotherapy treatment for AD. However, concerns regarding efficacy and undesired side-effects have led to the search for alternative sources of ChIs including those from natural sources. Phytochemicals can act as ChIs as well as possessing powerful antioxidant activities that could ameliorate the cellular redox stress observed in AD. In this study, the phytochemicals (4-O-cafeoylquinic acid (4-O-CQA), rutin hydrate, quercetin 3-β-D-glucoside (Q3D-β-G), and chlorogenic acid) were quantified via their ability to scavenge free radicals using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and lactate dehydrogenase (LDH) assays.

5. Phytocannabinoids display antiradical and neuroprotective effects against pesticide-induced neurotoxicity

Presenting author: Dr Ayman Alsaaadi (mxzxa24@exmail.nottingham.ac.uk)
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Keywords: Phytocannabinoid, Cannabidiol, Cannabidivarin, Cannabigerol, Antioxidant, Neurotoxicity, Chlorpyrifos-oxon, Malaoxon

Parkinson’s disease (PD) is a major neurological disorder characterised by progressive nervous system degeneration and loss of dopaminergic neurons within the basal ganglia. Neuroinflammation and oxidative stress contribute to the neuronal damage observed in PD. Phytocannabinoids may be neuroprotective via their antioxidant and/or anti-inflammatory activities. In contrast, pesticide exposure can induce neurotoxic effects, representing an environmental mechanism for the potential induction of Parkinsonian phenotypes. This study investigated the antioxidant and neuroprotective activity of the phytocannabinoids, Cannabidiol (CBD), Cannabidivarin (CBDV) and Cannabigerol (CBG) in response to the neurotoxicity and oxidative stress induced by the pesticides, chlorpyrifos-oxon (CPO) and malaoxon (MAL) in SH-SY5Y neuroblastoma cells. The relative antioxidant capabilities of the phytocannabinoids were quantified via their ability to scavenge free radicals using 2,2’-azino-di-(3-ethylbenzthiazoline sulfonic acid) (ABTS), 2,2-diphenyl-1-picrylhydrazyl (DPPH), and Ferric ion reducing antioxidant power (FRAP) assays. Pesticide effects on cell viability were evaluated using a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Phytocannabinoids exhibited useful free radical scavenging ability and were able to limit cellular redox stress induced by pesticides. Reduced cellular redox stress correlated with improved cell viability. These research findings provide evidence of the antioxidant and neuroprotective properties of phytocannabinoids that might provide a valuable means to treat acute pesticide-induced neurotoxicity.

6. The Gut-Brain Axis in Parkinson’s Disease: Linking Metagenomics and Host-Transcriptomics

Presenting author: Mr Rahul Arora (ra594@cam.ac.uk)
Authors: Arora R 1-3, Tomkins J 1 2, Almeida A 3, Vendruscolo M 1 2
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Keywords: Neurodegenerative Disorders, Ageing, Parkinson’s, Gut-Brain Axis, Transcriptomics, Metagenomics

Parkinson’s disease (PD) is the most prevalent neurodegenerative movement disorder, with symptoms that include bradykinesia, tremors, and rigidity. The disease is often associated with non-motor symptoms, in particular gastrointestinal complications, which manifest very early in the disease progression, often before diagnosis. Related to these observations, the composition of the gut microbiome has been linked to the incidence of PD, but the relationship between the microbiome and the molecular changes in the brain remains an enigma. To investigate this problem, we developed a computational pipeline for an integrated analysis of two different omics datasets. The pipeline is based on identifying ageing-associated transcriptomic signatures of the brain in combination with the characterization of the gut microbial diversity using shotgun metagenomic approaches. This framework could help tease apart the signals associated with healthy ageing and PD, thus aiding in a quantification of the disease progression with enhanced sensitivity.
Human Connectome Project, prefrontal cortex, cognitive control

Typical current TMS-fMRI setups have limited spatial resolution because of the need to accommodate the TMS coil, using a maximum of 14 radio-frequency (RF) MR channels. This limits whole-brain coverage and/or the quality of the imaging sequences. Precision fMRI sequences, like those from the Human Connectome Project (HCP), have revolutionized cognitive function imaging with their advanced anatomical clarity. These sequences were typically designed for 32-channel RF coils. Here we developed a new setup with two flexible RF coils enveloping the head and TMS coil, achieving a 22-channel system. This enabled us to leverage high-resolution HCP-style sequences. Preliminary data indicate that our setup surpasses existing benchmarks. Moreover, its high resolution enabled us to delineate the effects of single TMS pulses on closely positioned prefrontal cortex circuits. This novel setup promises a deeper insight into brain function, the neural underpinnings of TMS, and enhanced precision for clinical interventions.

8. Association of TMEM106B aggregates with human aging

**Presenting author:** Mehtap Bacioglu (mb2262@cam.ac.uk)

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**Keywords:** synucleinopathies, human aging, TMEM106B

**Objectives:** TMEM106B is a type II transmembrane protein linked to lysosomal function, and genetic variation at the TMEM106B locus has been implicated with disease risk in FTLD-TDP. As well as age-associated phenotypes, Cryo-EM has allowed to identify TMEM106B filaments in aged brains of individuals with or without a neurological disease (Schweighauser et al., 2022, Nature). Here we aimed to further characterize the distribution and localization of TMEM106B deposits in human brains and other tissues.

**Methods:** Paraffin embedded sections and fresh frozen material of brain and peripheral tissues from individuals with or without various neurodegenerative diseases were used. These included cases of beta-amyloidosis, tauopathies, synucleinopathies, TDP43 proteinopathies, Huntington’s disease, Friedreich’s ataxia, as well as neurologically healthy individuals, who were obtained from several brain banks. The presence and distribution of TMEM106B inclusions were studied by immunohistochemistry and immunoelectron microscopy of tissue sections, and by immunoblotting using anti-TMEM106B antibodies directed against different epitopes of the protein.

**Results:** We found inclusions of fibrillar TMEM106B in different brain regions without a clear link to disease. Instead, TMEM106B deposits were found to occur in an age-dependent manner, confirming our previous findings. We found that the inclusions primarily localized to astrocytes in the brain. Antibodies against an epitope containing the last 12 amino acids of TMEM106B failed to stain these inclusions, resembling instead the diffuse cytoplasmic staining of N-terminal-specific antibodies. Furthermore, TMEM106B inclusions were limited to the nervous system, as no staining could be observed in heart, liver, lymph node or spleen tissue sections. Our immunohistochemistry results were confirmed by immunoblotting of the sarcosyl-insoluble fractions.

**Conclusions:** TMEM106B inclusions are present predominantly in astrocytes and are limited to the nervous system. Their presence is associated with aging and is independent from the presence of neurodegenerative diseases. Further work will help to clarify the functional significance of TMEM106B inclusions in aging and disease.

9. Disease phenotypic screening in neuron-glia co-cultures identifies blockers of inflammatory neurodegeneration

**Presenting author:** Mr Timothy JY Birkle (tjyb3@cam.ac.uk)

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**Keywords:** Neuropharmacology, New Technologies, Neurodegenerative Disorders, Microglia, Neuroinflammation, Inflammation, High-content, Screening

**Neurophysiology and neuropathology are mediated by the interaction of neurons and glial cells, which cannot be modelled by monocultures. However, mixed cultures are difficult to use and analyse for high-throughput screening. Here, we show the utility of compound and target screening using primary neuron-glia cultures to model inflammatory neurodegeneration alongside live-cell stains and automated classification of neurons, astrocytes or microglia using open-source analysis software. Out of 227 compounds with known bioactivities, 29 protected against lipopolysaccharide-induced neuronal loss, including drugs affecting adrenergic, steroid, inflammatory and MAP kinase signalling. The screen also identified physiological compounds, such as noradrenaline and progesterone, that protected, and identified neurotoxic compounds, such as a TLR7 agonist, that induced microglial proliferation. Thus, combining automated image analysis of complex cultures with high-throughput screening of known compounds in a cellular model of disease allows identification of important biology, as well as potential targets and drugs for treatment.**

10. Validation of alpha-synuclein antibodies using quantitative bioimaging

**Presenting author:** Mr Jonathan C Breiter (jcb228@cam.ac.uk)

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**Keywords:** Neuropharmacology, Neurodegenerative Disorders, Neuroregeneration

**Antibodies are a ubiquitously used tool in biomedical and neuroscientific research to probe for specific proteins of interest in complex samples. Similarly, antibodies targeting the proteins implicated in neurodegenerative diseases, like alpha-synuclein, amyloid beta or tau, are frequently utilised to visualise and quantify these proteins’ location and quantity in brain. The usage of antibodies in biomedical research rests on the assumption of selectivity of these antibodies in a complex sample. This means that**
the antibody is perfectly selective in binding only to the protein of interest, and not any other proteins. Recent evidence points out low levels of specificity and selectivity of multiple alpha-synuclein antibodies using biophysical methods. We address the unmet need to identify off-target binding quantity of alpha-synuclein antibodies in brain tissue using a novel high-throughput quantitative imaging strategy which offers high sensitivity down to the nanometer level. We show that multiple alpha-synuclein antibodies show off-target binding in SNCA knockout mouse brain, implicating the need for better antibody selectivity quantification and improvement of existing probes for alpha-synuclein.

11. Non-pharmacological interventions in the management of dementia-related psychosis

Presenting author: Miss Alice Burnand (a.burnand@ucl.ac.uk)

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Keywords: Neurodegenerative Disorders

Introduction: It is estimated 20-70% of those living with a dementia diagnosis experience dementia-related psychosis (D-RP). D-RP results in decreased quality of life, increased care burden, increased rapid cognitive decline, hospitalisation, and earlier care/nursing home admission, all which come at a considerable cost to the NHS. Atypical antipsychotic medications are typically used to treat hallucinations and delusions in those with dementia but have short-term efficacy and are often associated with sedation, falls, extrapyramidal effects, and worsening cognition. Effective dementia-related psychosis management with the use of non-pharmacological intervention could safely improve the quality of life of those living with dementia, as well as reduce care burden and burden on health services.

Aims: To evaluate the effectiveness of non-pharmacological interventions in the management of dementia-related psychosis.

Studies that use objective measures of non-pharmacological interventions on patient or caregiver quality of life, or determine the cost-effectiveness and safety of non-pharmacological interventions against antipsychotic medications will also be included.

Design: A global systematic literature review is being conducted in Medline, Embase, PsychINFO, CINAHL, Web of Science, and CENTRAL for studies of non-pharmacological management of psychosis in people living with dementia, published in any language. The studies that meet the predetermined inclusion criteria will be summarised using meta-analysis or narrative synthesis, depending on the heterogeneity of interventions and outcomes.

Searches have been developed and will be carried out, with full text screens yielding 18 papers to be included. The protocol is registered with PROSPERO [ID: CRD42022294750] and the review will be completed by November 2023.

Design: Data extraction of 18 included papers is currently being undertaken (July 2023) and results will be published at the conference.

12. Visual Impairment Across Dementia Subtypes: Insights from High-Density Diffuse Optical Tomography

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Keywords: New Technologies, Neurodegenerative Disorders

Markers of brain oxygenation may aid the early detection of dementia given the implication of vascular abnormalities in the development of the disease. Near-infrared spectroscopy (NIRS) can provide measures of brain oxygenation by exploiting the differing absorption spectra of oxygenated (HbO) and deoxygenated haemoglobin (HbR). Considering the range of visual symptoms observed in dementia, markers of visual function may be particularly valuable, however no studies have yet explored this using NIRS. To do so, we used High-Density Diffuse Optical Tomography (HD-DOT) to measure cortical responses to visual stimulation. HD-DOT combines high-density NIRS arrays with anatomical information to produce detailed, volumetric maps of brain oxygenation. HD-DOT data was collected using the Lumo (Gowerlabs Ltd) which consisted of 6 tiles (18 sources and 24 detectors) covering the bilateral visual cortex. A radial checkerboard reversing at 7.5 Hz was presented to both hemifields, for a total of 18 10 s stimulation blocks interleaved with 15 s rest periods. Optode and cranial landmark locations were obtained using photogrammetry [1]. The data was pre-processed, and images were reconstructed using the DOT-HUB toolbox [2]. Preliminary data is presented from healthy ageing and Alzheimer’s Disease (2M, mean age = 72 ± 0). Visual stimulation elicited visibly reduced concentration changes for both HbO and HbR for both hemifields in Alzheimer’s Disease compared to the healthy control.

These preliminary results indicate that using this paradigm with HD-DOT may be able to discriminate between healthy ageing and dementia, with confirmation upon statistical analysis and further data collection. Future work includes incorporating the individuals’ structural MRIs to ensure that changes in light attenuation caused by cortical shrinkage are not misattributed to functional changes.


13. Objective measures of gut dysfunction in Parkinson’s Disease

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Keywords: Neurocognition, Neurodegenerative Disorders, Parkinson’s disease; gut-brain axis; constipation; gastrointestinal

Objective: To characterize gastrointestinal (GI) dysfunction in Parkinson’s disease (PD) using objective measures. Background: GI dysfunction is an important feature of PD and may play a role in disease onset and progression. However, studies often involve only self-reported questionnaires hindering accurate estimates of prevalence. Methods: 75 participants with PD (PwP) and 59 paired household controls (HC) ingested a blue food dye to measure GI transit time (length of time between ingestion of the dye and first appearance of blue stool). PwP also completed the Gastrointestinal Dysfunction Scale - Parkinson’s Disease (GIDS-PD). In a small pilot study, 5 PwP and 5 household controls underwent a Small Intestinal Bacterial Overgrowth (SIBO) breath test that measures gases produced in the gut; hydrogen and methane.

Results: There was a significant difference in gut transit time between PwP (61.5 - 41.6 hours) and household controls (37.8 - 26.9 hours, p<0.001). 29 PwP and 8 HC met...
14. Alpha-synuclein condensate formation in cells - Effect of Parkinson's disease variants

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Keywords: Neurodegenerative Disorders, alpha synuclein, phase separation

Alpha-synuclein (aSYN) is a neuronal protein that is implicated in the pathogenesis of several neurodegenerative disorders including Parkinson’s disease (PD). aSYN binds to synaptic vesicles under normal physiological conditions, but a major fraction also exists in solution in its intrinsically disordered form. Multiple cellular conformations of aSYN have been reported, the intrinsically disordered monomer, physiological and pathological oligomers and fibrillar aggregates. Recently, aSYN has been shown to undergo liquid-liquid phase separation (LLPS) resulting in the formation of droplet-like condensates in vitro and in mammalian cells. Previous research in our lab has led to the identification of VAMP2 as a regulator of aSYN condensate formation. Using an aSYN-VAMP2 co-expression model in HeLa cells, our current work investigates the effect of PD-related aSYN variants on the ability of aSYN to form condensates. We have found that several aSYN variants including A30P, G51D, A53E and A30G do not form condensates upon co-expression with VAMP2, whereas other variants like A53T, E46K, E83Q and H50Q readily form condensates at levels comparable to, or greater than the wildtype protein. Intriguingly, this pattern broadly correlates with the lipid binding capabilities of the different variants previously reported in the literature. Additionally, data from in vitro experiments performed in our lab using recombinant aSYN and synthetic lipid vesicles, indicate that lipid membranes increase the extent of aSYN LLPS. These observations lead us to hypothesize that lipid surfaces may act as substrates for the nucleation and formation of aSYN condensates. Future work will focus on further characterization of aSYN variants which undergo LLPS and their co-localization with cellular membranous organelles like mitochondria, ER or endo-lysosomal vesicles.

15. ‘Junk-DNA’ mining: Deciphering the evolutionary dynamics of GABRA1, GABRA4 and GABRA5 in vertebrate introns

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Keywords: Neuropharmacology, New Technologies

The GABAR (Gama Amino Butyric Acid type A Receptors) are the major inhibitory neurotransmitter receptors found in the CNS of vertebrates. These ligand-gated ion channels are composed of hetero-pentameric assembly of multiple subunits of α, β and γ. Despite their conservation across vertebrate species, little is known about the evolutionary process that has modelled them. Through the use of different bioinformatic tools, the study investigated the evolution of introns and their relationship to the GABRA1, GABRA2 and GABRA5 gene structure and trends within organism complexity. The study showed that the intron sizes in these subunits cannot be associated as a definitive parameter to explain trends in evolution from lower to higher vertebrates. The dot plots and phylogenetic trees generated indicate that the intron has undergone different evolutionary constraints in comparison to exons. Understanding the variations of structural characteristics of introns across vertebrate species can influence the expression of these subunit genes that have major clinical implications in numerous neurological processes.


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Keywords: New Technologies, Neurodegenerative Disorders, microscopy, plasmonics, alzheimer’s, detection

Background: Amyloid-beta (Ab) protein aggregates have been implicated in the pathology of Alzheimer’s disease (AD). These aggregates are difficult to characterise due to their small size, requiring very sensitive techniques. Gold Nanoparticles (AuNPs) form plasmonic cavities when in close proximity to a gold surface. The cavity both enhances and scatters incident light, with a resonant wavelength strongly dependent on the size of the cavity. These plasmonic cavities were used to detect and size Ab aggregates at ultra-low concentration using darkfield spectroscopy. Methods: AuNPs were coated with the Ab specific 6E10 capture antibody, incubated with a synthetic aggregate sample, and centrifuged to isolate the AuNPs. They were then placed on a gold surface, and darkfield scattering spectra were obtained. The peak scattering wavelengths for each AuNP were used to produce a histogram of gap sizes, and thus the size distribution of detected protein aggregates. Results: Significant differences were seen in resonant peak position between monomeric samples of Ab and 24 hour aggregated samples. This allows for easy identification of protein monomer vs fibrillar aggregates. In the case of aggregates, some peaks in the darkfield scattering spectra also appeared strongly polarised, suggesting dimerisation of the AuNPs. These was not present for the case of monomeric sample. Conclusions: With this novel technique it was possible to clearly distinguish between samples of Ab monomer and aggregates. This approach can likely be expanded to find the range and proportion of aggregate sizes in serum samples to detect the onset of AD. The AuNP dimerisation when Ab aggregates are present is also interesting, and may serve as further verification of the size or shape of these aggregates.
17. Inflammation and Neuropsychiatric Symptoms in Frontotemporal dementia and related disorders

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Keywords: Neurodegenerative Disorders, Frontotemporal Lobar Degeneration, Inflammation, Neuropsychiatric Symptoms, Cytokines

Neuroinflammation is related to multiple neurodegenerative and psychiatric conditions. Patients with dementia often present psychiatric symptoms, which are associated with high mortality and cognitive decline. Here we investigated the relationship between inflammation, measured by serum cytokine levels, and neuropsychiatric symptoms in frontotemporal dementia (FTD) and related disorders. Our hypothesis was that elevated cytokine levels correlate with more severe neuropsychiatric symptoms. We included 171 participants recruited at the Cambridge Centre for FTD. 41 cytokines were measured in serum samples, of which 26 were detectable in most participants. Cytokine concentrations were log-transformed and compared between patient groups and healthy controls using t-tests and Mann-Whitney U tests. Spearman’s correlations assessed the association between cytokines and behavioural changes. Principal Component Analysis (PCA) was used to reduce the dimensionality of log-transformed cytokine data, revealing two components. Component 1 loaded onto proinflammatory cytokines (TNF-R1, TNF-alpha, M-CSF, IL-12, IL-17A, YKL-0, IL-6, hs-CRP, and IP-10); higher proinflammatory cytokine levels correlated with poorer cognition. Component 2 was loaded on MCP1, MCP4, and TARC chemokines; high chemokine levels were associated with depression and apathy. The results show cytokine patterns associated with cognition and neuropsychiatric symptoms in FTD and related conditions. Immunotherapeutic strategies warrant further evaluation and clinical trials as a potential route to symptomatic and/or disease-modifying benefit.

18. The Interplay between ER Structure and Functional Calcium Signaling in Astrocytes

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Keywords: Neuroglia, calcium signals, endoplasmic reticulum

Astrocytes generate Ca²⁺ signals in response to specific stimuli, which are pivotal for their functional performance. These Ca²⁺ events are majorly powered by its releases from the endoplasmic reticulum (ER). Morphological perturbations in the ER and alterations in Ca²⁺ patterns are associated with brain diseases. Prompted by this, we investigate the role of the ER’s tubular structure (and its integrity) in determining the precise amount, timing, and location of Ca²⁺ supply within the complex architecture of astroglial cells. Utilising a toolkit tailored for ER structure manipulation and combined with live-cell imaging of ER transport and Ca²⁺ dynamics, we discerned the intricate relationship between ER morphology and its Ca²⁺ handling capabilities. This understanding was deepened by in-silico simulations, which predicted fluid dynamics across different ER configurations. Our results reveal principles and a mechanism by which ER morphology modulates local Ca²⁺ releases. These findings help understanding the optimal ER structure for varied physiological states and shed light on the pathologies associated with changes in ER form and Ca²⁺ signal patterns. Ultimately, our research highlights the link between ER morphology and the effective functioning of astroglial cells and suggests potential manipulation nodes to improve astroglia performance.

19. Endoplasmic Reticulum morphology affects neuronal function

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Keywords: Neuroregeneration, neurophysiology, calcium, endoplasmic reticulum

The Endoplasmic Reticulum (ER) in neurons extends from the soma to dendrites and axons, maintaining its morphology and continuity over long distances thanks to several ER-shaping proteins. Mutations in some of these ER morphogens cause Hereditary Spastic Paraplegia (HSP), a neurodegenerative disorder that affects long corticospinal motor axons. The cellular mechanisms linking ER to this disease are still not understood. We study how the morphology of the ER is related to neuronal health by assessing the effect of ER structural manipulation on its function. Previous studies from our group show a link between ER shape and ER calcium dynamics in non-neuronal cells. Building on these results, we focus on how ER shape influences neuronal functions that depend on ER calcium. We have shown that Reticulon 4a regulates neurite outgrowth in human induced pluripotent stem cell (hiPSC)-derived neurons through limiting calcium release critical for this process. We also observe that this process is affected by manipulating ER structure through other ER-shaping proteins. Further, investigating the consequences of ER morphology modulation on network neurophysiology in hiPSC-derived neurons, we observe a series of significant effects: these cells exhibit spontaneous synchronous synaptic activity-dependent calcium bursts, the pattern of which is closely linked to ER structural alterations. We demonstrated that ER calcium is necessary to support these calcium waves, using selective inhibitors, including those targeting SERCA pumps, IP3 and Ryanodine Receptor. In summary, our study confirms the role of the ER in neuronal calcium bursts, defining their pattern, consistent with our model describing the ER functioning as a calcium supply system sensitive to the arganellae’s morphoregulation.

20. FOXG1 controls early developmental tissue architecture in neural monolayer and organoid models

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Keywords: Neuropsychiatry - Autism, New Technologies, Neurodevelopment, transcription factor, cerebral organoid
FOXG1 is a transcription factor that is important for brain development. Mutations in FOXG1 perturb forebrain development and are commonly associated with neurodevelopmental conditions such as autism and epilepsy. By studying the biological functions of FOXG1 and providing mechanistic insight into how it functions, we can derive a better understanding of the molecular and cellular aetiology of these neurodevelopmental conditions. This will help us to identify new diagnostic and treatment targets to improve the care of patients with these conditions. FOXG1 is expressed in neural stem cells (NSCs). Here, FOXG1 has been hypothesised to control the balance between proliferation and differentiation by controlling cell-cycle and expression of neuronal lineage genes. To test this, we differentiated induced pluripotent stem cells (iPSC) into neural precursor cells using neural monolayer and organoid models. This revealed that FOXG1 has important biological functions at the earliest stages of neurodevelopment, earlier than previously reported. Specifically, we show that FOXG1 is required to form neural rosette structures (an in-vitro 2D neural tube correlate). Loss of FOXG1 disrupted rosette formation and caused misexpression of key neural markers. Furthermore, initial data suggests our findings are replicated in 3D brain organoid models, which are better able to recapitulate brain development. This raises the possibility that atypical traits originate very early on during brain development. We are now taking this work forwards by studying how FOXG1 controls enhancer-promoter communication and transcriptional activity in neural rosettes, and by studying the effects of specific FOXG1 mutations.

21. Linking glycosphingolipid imbalances to changes in the plasma membrane proteome: new mechanisms driving neurodegeneration

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Keywords: New Technologies, Neurodegenerative Disorders, childhood disease
Glycosphingolipids are an important class of lipids enriched in the outer leaflet of the plasma membrane. Disorders that alter glycosphingolipid metabolism cause devastating neurodegenerative and demyelinating diseases. We have identified that deletion of the glycosphingolipid metabolising enzymes GALC or UGT1 cause significant changes to the abundance of specific plasma membrane proteins, several of which are implicated in degenerative brain disease. We have extended this discovery by characterising the specific interaction of the membrane protein Neurofascin with the glycosphingolipid sulfatide and determining the structure of the extracellular domain of NF155. This work reveals that NF155 binds multiple sulfatide molecules allowing it to bind flat along its own membrane explaining its sensitivity to altered lipid composition. This is the first identification of specific changes to proteins at the plasma membrane caused by sphingolipid-mediated disease and provides important insights into new mechanisms driving demyelinating neurodegenerative diseases.

22. Remyelination requires microglia activation and transient decline in neuronal activity

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Keywords: Neurodegenerative Disorders, Myelin, remyelination, Multiple Sclerosis
Remyelination requires neuronal activity, however the mechanisms underlying the interplay between remyelination and activity are poorly understood. Using a model of focal demyelination, we show that loss of myelin leads to a transient decline in neuronal activity and that preventing changes in activity following demyelination decreases the efficiency of remyelination. This transient decline in activity coincides with the peak of oligodendrocyte precursor cell (OPC) proliferation in the remyelinating white matter and increasing activity during this period reduces the number of proliferating OPCs. Investigating on the mechanisms underlying changes in neuronal activity, we found that following demyelination, microglia numbers increase in the grey matter and that synaptic terminals are engulfed by activated microglia, resulting in grey matter synaptic loss. These changes are likely to be required for myelin regeneration, as remyelination levels are decreased when microglia are depleted in the grey matter. Taken together our data suggest that microglia activation in the grey matter is followed by a transient decrease in neuronal activity play a relevant role in the regeneration of myelin in the white matter.

23. Brains in focus: Uncovering protein aggregate changes across Alzheimer’s disease with single-molecule imaging

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Keywords: Neurodegenerative Disorders, Aggregation, Tau, Microscopy, Fluorescence, Super-resolution, Post-mortem, Brain
Brain-derived protein aggregates remain largely uncharacterised due to their solubility, low biological concentration, small size, and structural heterogeneity. This explorative study increases our understanding of aggregate changes across Alzheimer’s disease (AD). Post-mortem brain samples spanning all AD stages and two regions, middle temporal gyrus (MTG) and primary somatosensory cortex (SOM), were obtained from 13 donors. Soluble and insoluble brain proteins were extracted in liquid fractions for single-molecule studies. Our ultra-sensitive aggregate-specific Simoa® assays detected exponential increases in total and phosphorylated tau (p-tau) aggregate quantity from mid-stage AD, enabling earlier AD-associated aggregate detection in SOM compared to traditional immunohistochemistry-based Braak staging. Region-specific differences were identified: MTG aggregate quantity showed earlier, steeper increases than SOM, with >1000-fold difference between regions in late-stage AD. HT7+ and AT8+ aggregates were highly correlated (R2>0.99) in both regions with Simoa®, supporting evidence of association between tau aggregation, phosphorylation, and AD stage. The proportion of tau aggregates with multiple phosphorylation sites was ~5-10% in non-AD controls increased to ~20-50% in late-stage AD donors (~SOM-MTG regions).
respectively, as measured by A18-T181 colocalisation single-molecule pull-down (SiMPull) assays. SiMPull assays with super-resolution microscopy uncovered aggregate size and shape information: fibril-shaped tau aggregates of greater sizes were detected in late-stage AD cases, in MTG not SOM. Overall, detailed region-specific AD-associated differences in tau aggregate quantity, phosphorylation and morphology have been determined. More work is required to understand the links between these changes and their association with AD symptomology.

24. Is motivation toward a reward a predictor of dysfunctional behaviour?

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Keywords: Neurocognition, Neuropsychiatry - Addiction, Sign-tracking, OCD, Addiction

Introduction: When presented with a reward-related conditioned stimulus, individuals vary in their responses. Depending on whether they approach the location of a reward delivery or the cue itself, they are classified as goal- or a sign-trackers respectively. We have previously observed a correlation between sign-tracking and dysfunctional, compulsive-like checking on the Observing Response Task (ORT). As sign-trackers have also been reported to show more rapid progressions to compulsive-like drug-seeking and to rely more upon habitual-like model-free learning, then this may indicate that sign-trackers rely more on habitual learning. Whether this association is specific to sign-tracking, or could be observed with other measures of motivated behaviour, such as pavlovian-instrumental transfer (PIT) remains unknown. Thus, we aim to test whether sign-trackers and goal-trackers show differential performance on both specific PIT (which relies on model-free learning) and general PIT (which relies on model-based learning), and whether PIT performance can be similarly related to dysfunctional checking on the ORT. Methods: Rats will be trained on a Pavlovian-Instrumental Transfer task with two separate reinforcers, two responses and two reward-associated cues (and a third, neutral cue). General and specific PIT will be assessed in a probe test, before rats are subsequently trained on both pavlovian autoshaping (to classify the animals as goal- and sign-trackers) and the ORT. Statistical Analysis: We will analyze the mean lever presses from the PIT test data using an ANOVA and the ORT task using mixed 2x2 ANOVAs. In our study, we expect that ST will have a greater general PIT effect than GT, which will positively correlate with dysfunctional checking during the ORT task. Whether PIT performance can be similarly related to dysfunctional checking on the ORT. Methods: Rats will be trained on a Pavlovian-Instrumental Transfer task with two separate reinforcers, two responses and two reward-associated cues (and a third, neutral cue). General and specific PIT will be assessed in a probe test, before rats are subsequently trained on both pavlovian autoshaping (to classify the animals as goal- and sign-trackers) and the ORT. Statistical Analysis: We will analyze the mean lever presses from the PIT test data using an ANOVA and the ORT task using mixed 2x2 ANOVAs. In our study, we expect that ST will have a greater general PIT effect than GT, which will positively correlate with dysfunctional checking during the ORT task.

25. MEG markers of consciousness in early Alzheimer’s disease

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Keywords: Neurodegenerative Disorders, Alzheimer’s Disease, Consciousness, Lempel Ziv, Complexity, Arousal

Studies exploring the spatiotemporal complexity of the EEG signal in Alzheimer’s Disease (AD) have demonstrated that people with AD exhibit significantly lower Lempel Ziv (LZ) complexity values compared to healthy controls. While this evidence has been demonstrated using analytic approaches such as sample entropy, it remains an important clinical question as to how this relates to the clinical features or phenomenology of AD, specifically cognitive decline. This study analysed MEG/EEG data collected continuously at a 1 kHz sample, eyes closed resting state, from 2 to 13.35 mins. To assess the level of consciousness, the LZ complexity was used as a marker for the richness of content. Arousal was measured using a ratio of the whole brain alpha-theta bands. A total of 166 participants were included, 83 with AD and 83 controls. Results showed that the mean LZ sum value was significantly greater in the controls compared to AD (0.590 vs 0.581, W = 4171, p = 0.025). The mean alpha-theta ratio was significantly less in controls compared to the AD (1.041 vs 1.372, W = 2728, p = 0.021). Regression analyses to investigate the association between the Mini-Mental State Examination (MMSE) and LZ/alpha-theta showed that MMSE was associated with a significant increase in LZ sum (0.003, t = 3.033, p = 0.003), indicating an increase in complexity/consciousness, and with a significant decrease in the alpha-theta ratio (-0.102, t = -2.595, p = 0.011), indicating increased drowsiness. In conclusion, this study found that AD patients had reduced consciousness level and arousal compared to age-matched healthy controls and that they correlated with severity of the disease, as measured by the MMSE. This provides further insight into the neurophysiological changes associated with AD. While more research is needed to better understand the relationship between EEG and the clinical features of AD, this study represents an important step forward in the development of new diagnostic tools.

26. Interrogation of a novel human 3D organoid corticospinal injury model to discover and validate targets promoting regeneration

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Keywords: New Technologies, SCI, spinal cord injury, organoids, stem cells, human models

Treatments to evoke repair and reconnection between corticospinal axons and their targets are vital to restoring function following spinal cord injury (SCI). Research in rodents has discovered that this failure to regenerate is due to ‘roadblocks’ either relating to intrinsic properties of the neuron itself or due to extrinsic factors in the hostile environment around the lesion. However, a lack of human model systems has hindered the translation of therapeutic approaches. To overcome this limitation, we have developed a novel 3D human corticospinal-motor axis system to address this need. Using a combination of single-cell transcriptomics, spatial immunolabelling tools and functional electrophysiological assays, we show a recapitulation of the anatomy and function of human corticospinal circuitry. Exposing this platform to axonal tract injury, we predicted potential gene networks orchestrating regenerative pathways. The pharmacological inhibition of PTEN, one of the elements
of this network, combined with 2-photon live-imaging and histological approaches, demonstrated increased axon growth cone dynamics. In summary, our model provides a human translational discovery and drug-testing platform relevant to spinal cord regeneration.

27. Peripheral and central immune changes in early PD: baseline analysis of the AZA-PD trial cohort

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Keywords: Neurodegenerative Disorders, Parkinson’s disease, immune system.

Background: There is increasing evidence implicating the immune system in the progression of Parkinson’s Disease (PD). We are therefore conducting a clinical trial repurposing azathioprine, an immunosuppressant drug, with the aim of slowing down the progression of PD. AZA-PD is a randomised placebo-controlled, double-blind phase II trial in patients with early PD, with no immune comorbidities. In our participants we are performing a detailed characterisation of the immune profile in the blood at multiple timepoints, with a subset also donating cerebrospinal fluid (CSF). In addition, we have recruited a group of age-matched healthy controls. Methods: Immune cells were separated from blood and CSF and labelled with fluorescently-labelled antibodies specific to key immune markers. Flow cytometry was used to characterise key cell types. The immune profile in early PD (AZA-PD baseline visit- pre-treatment) was compared to age-matched controls. Results: Analysis was performed on blood in 61 patients with PD (mean age 66.16, SD 7.24) and 52 controls (mean age 68.52, SD 6.74). PD patients had a higher neutrophil to lymphocyte ration (p=0.027) and showed a shift towards a pro-inflammatory monocyte phenotype. PD had a higher proportion of classical cells (p=0.046) and a reduction in anti-inflammatory T cell populations, including TH2 (p=0.023) and CD8+Tregulatory cells (p=0.010). CSF was collected from 35 patients with PD and 8 controls. There were no differences seen in numbers or phenotype of immune cells between groups. In both PD and controls there was a higher expression of CD28 on T cells in the CSF compared to blood (p<0.001), with a higher proportion of effector cells (p<0.001). Conclusion: The immune profile in the periphery is more inflammatory in early PD than controls, and differs in CSF versus blood, with a preferential recruitment of effector cells. This suggests that peripheral immunity may influence central brain pathology.

28. Assessing the Privacy Risk of AI Research which uses Neuroimaging and Genomic Data within Trusted Research Environments

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Keywords: New Technologies, Neurodegenerative Disorders, Artificial Intelligence, Neuroimaging, Privacy, Trusted Research Environments.

The Dementias Platform UK Data Portal is a Trusted Research Environment (TRE) which has recently developed a world leading neuroimaging data repository and analysis environment with linkage to genomics and health data. With this, we have seen a surge of applications for AI research which has forced us to review our release assessment criteria for determining whether a project's outputs are safe to be taken out of our secure environment. AI has added a level of complexity to this due to certain models inherently containing data within them and the potential to be attacked, therefore creating the possibility of sensitive and protected data being leaked. This poses a risk for TREs as data is never allowed to be released into the public. However, we cannot completely ban the release of AI models all together as this is important research with the potential of being implemented into clinical healthcare systems. This has led us to create an AI Privacy Risk Index to aid in the assessment of AI models which also includes the implementation of a suite of tools for determining whether an AI model suitably protects the privacy of the individuals used to train the model. This index is informed by a range of researchers, policymakers, data providers and the public to get a well-informed view of what people are most concerned about and what mitigations they think are the most acceptable. Tools are also implemented to determine the disclosure risk of the data used to train the model, whether an AI model is susceptible to attack and whether a model overfits which feeds into the AI Risk Index. This allows us to be able to assign a score to a model depending on the data that was used to train it, what problems there might be in the model, whether the model has implemented any privacy-preserving techniques and what environment will that model be released in.

29. First Steps in Using Topographic Deep Artificial Neural Network Models to Generate Hypotheses about Not-yet-detected Functional Neural Clusters in the Ventral Stream

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Keywords: Neurocognition, object vision, inferior temporal cortex, topography, selectivity, dimensionality.

Although several types of spatially-aggregated neural functional selectivities have been reported in the inferior temporal (IT) cortex of humans and monkeys, such as face, place, and body selectivities, broad swaths of IT have yet to be similarly characterized. Here, we present the first steps of using Topographic Deep Artificial Neural Networks (TDANNS) as hypothesis generators of not-yet-detected spatially-aggregated IT functional selectivities. To isolate the shared selectivities across a population of TDANNS, we applied hyperalignment to the IT layer of ten TDANNS. We then analyzed the shared underlying functional representations to identify eleven predicted neuronal functional selectivity clusters. After mapping these clusters back to the spatial IT maps in each TDANN, we find that face-selective units - which spatially aggregate in TDANNS - are strongly loaded on one of these functional clusters. On visual inspection, the other functional clusters appear to be selective for scenes, animal bodies, and mid-level object properties. Topographic ANNs, when analyzed in this manner, could be used to predict novel spatially-aggregated selectivities shared by all brains and to predict the spatial relationships between those functional aggregates. Both types of predictions could then be tested via targeted fMRI experiments.
30. Managing the needs and symptoms of residents living with Dementia in care homes through music therapy: A non-randomised feasibility trial

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Keywords: Neurodegenerative Disorders, Dementia, Music Therapy, Needs, Cognition, Neuropsychiatric symptoms, Care homes, Care quality

There is a growing need for evolving therapeutic interventions in care homes for residents living with dementia to manage the needs and symptoms of residents and enhance care quality. Music4theMind is a PhD research project at Anglia Ruskin University in collaboration with Anchor Care Homes with funding from The Utey Foundation to implement 12 weeks of music therapy in eleven care homes. The music therapy intervention consists of 2 weekly 1:1 sessions for 4 residents and an open weekly group session. It also incorporates skill sharing between care staff and music therapists at four-time points. To evaluate the feasibility and effectiveness of music therapy in care homes, initially, there will be two groups (6 intervention homes/5 traditional care). A range of clinical, organisational, and economic outcomes will be measured in all homes, pre- and post-12-week conditions. The primary outcome measure is met/unmet needs. After data has been collected, the homes in the traditional care group will then go on to receive the music therapy intervention. The aim is to help create a sustainable pathway to music therapy in care homes for people living with dementia to manage and support residents’ individual needs and symptoms and support staff in delivering quality care.

31. An Alzheimer’s disease blood-brain barrier model using microfluidic and iPSC technology to investigate BBB mechanics

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Keywords: Alzheimer’s disease, Blood-brain barrier, Microfluidics, Mechanobiology, Tissue engineering

Cerebrovascular disease accompanied by blood-brain barrier (BBB) disruption is one of the key pathophysiological hallmarks of Alzheimer’s disease (AD) with over 80% of patients with AD showing vascular pathology. In this project, we aim to develop an in-vitro model mimicking the BBB during AD with the purpose of investigating whether BBB mechanobiology contributes to AD-associated BBB disruption. Following the protocol from Prof. Kamm (MIT), we have established a healthy BBB microvascular network within fabricated microfluidic chips. Human iPSC-derived endothelial cells as well as human primary astrocytes and pericytes are combined into a fibrin hydrogel to assemble similarly as in-vivo. We and the Kamm lab have shown three-dimensional BBB-like interactions between vascular and stromal cells as well as the expression of genes important for BBB functioning, giving us confidence in the validity of our system in modelling the healthy human BBB. The Wray lab has previously derived astrocyte progenitor cells from familial AD patients with PSEN1 mutations as well as from healthy individuals. These cells offer a unique advantage, as typical human AD features (e.g. altered amyloid-β secretome) are present. We have incorporated these astrocytes into our model and were able to not only show survival of these cells but also connections between iPSC-derived astrocytes and vasculature. Further investigations of whether typical AD-associated BBB changes are found within the model and how familial AD-derived astrocytes influence microvasculature networks are currently being performed. Our final aim is to investigate tissue mechanics at the BBB. Our lab has recently shown that stromal cells can impact vascularization by altering tissue stiffness. We are interested in whether pathological hallmarks seen at the BBB during AD are also associated with altered tissue mechanics and whether altering typical mechanobiology pathways may revert some of the hallmarks of BBB dysfunction in BBB.

32. Object processing is shaped by expectations about the environment

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Keywords: Neurocognition, MEG, object perception, MVPA

We live in a complex environment in which context shapes expectations about the kind of things we might see. For example, we would be startled to encounter a donkey inside a house but not when we see one in a field. But in both cases, we know it’s a donkey - yet the neural processes that allow us to recognize the item as a donkey might be different. Research has established that objects which occur in a congruent context are recognized faster and more accurately than objects which occur in an incongruent context. However, it is still not known in what way context impacts object recognition. Does the preceding environment create expectations that modulate the neural representations of objects? Here, we use Magnetoencephalography (MEG) and multivariate pattern analysis (MVPA) to address the critical question of how expectations elicited by a scene affect the subsequent processing of an object. We recorded MEG while (n = 32) participants performed a speeded object recognition task. On each trial a scene and an object were presented separated by a blank screen. In total, 150 everyday objects were presented in consistent, inconsistent, and neutral contexts. We decoded the scene context at each time point to track how the expectations elicited by the context form and how they impact the neural patterns representing the objects. Our results show (1) that in contrast to the neutral context, both the consistent and inconsistent context elicit expectations about what objects might appear, and (2) that these expectations affect the neural representations of subsequently presented objects. The current findings demonstrate that objects are processed differently in the brain depending on our expectations. The contexts in which we encounter objects impacts the object’s neural representations.

33. Decreased alertness changes brain functional organization in passive movie-viewing

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Keywords: Neurocognition

Decreased alertness is associated with poor behavioural performance and brain function. While these effects have been shown in event-locked studies, it is unclear how...
decreased alertness affects brain function in sustained passive tasks. Naturalistic movie-viewing consistently recruits task-related brain networks, including those involved in low-level sensory processing and high-level integration. We speculated that 1) brain functional organization during passive movie-viewing depends on alertness level, and 2) these differences in functional organization are reflected in high-level functions of the visual attention network, as well as subcortico-cortical dynamics. We analyzed the Human Connectome Project 7T Functional Magnetic Resonance Imaging Database, in which 143 healthy adults viewed one hour of movie clips in the MRI scanner. Subjects’ data were classified post hoc as ‘alert’ or ‘drowsy’ according to a support vector machine algorithm that was applied on 60-second data segments. Then, we performed an inter-subject functional connectivity (ISFC) analysis, in which subjects’ brain activity was correlated with each other. We found that subjects’ brain activity was most strongly correlated in primary visual and auditory regions. The drowsy state had increased long-range functional connectivity in the visual attention network, as well as increased subcortical and cortical connectivity with supplementary eye fields and superior colliculi. During the alert state, we found stronger ISFC among default mode network regions. This work underscores the importance of accounting for alertness level when characterizing brain function. We show that passive viewing during drowsiness is enabled by increased functional connectivity among high-level regions of the visual attention brain network. More broadly, we show how subjects can be dynamically grouped according to state-level variations to understand how brain mechanisms can naturally change over time within an individual.

34. Detecting α-synuclein aggregates with small molecules on Single-Molecule Array

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Keywords: New Technologies, Neurodegenerative Disorders

Single-Molecule Array (SiMoA) is an ultra-sensitive, single-molecule detection technique capable of detecting analytes down to sub-femtomolar concentrations. Antibodies play an important role in SiMoA because they are used to form an immunocomplex by capturing and detecting targets-of-interest in situ. Although antibodies can specifically bind to targets with high affinity, the production and screening of antibodies are laborious and expensive. Also, it is sometimes difficult to raise antibodies to weakly immunogenic epitopes. Therefore, small molecules can be an alternative to antibodies. Structures of small molecules can easily be computationally simulated and optimised to target different proteins. The optimisation of small molecules can then be chemically synthesised in test tube with high predictability, quality, and reproducibility. We herein present strategies using small molecules to capture and detect aggregates of α-synuclein, which is believed as a biomarker of Parkinson’s disease, on SiMoA.

35. Theory of Mind at the Interface of Neuroscience & AI

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Keywords: artificial intelligence; cognitive and neuroscience; human theory of mind; inverse reinforcement learning; machine theory of mind.

Theory of Mind (ToM)—the ability of the human mind to attribute mental states to others—is a key component of human cognition. In order to understand other people’s mental states or viewpoint and to have successful interactions with others within social and occupational environments, this form of social cognition is essential. The same capability of inferring human mental states is a prerequisite for artificial intelligence (AI) to be integrated into society, for example in healthcare and the motoring industry. Autonomous cars will need to be able to infer the mental states of human drivers and pedestrians to predict their behaviour. In the literature, there has been an increasing understanding of ToM, specifically with increasing cognitive science studies in children and in individuals with Autism Spectrum Disorder. Similarly, with neuroimaging studies there is now a better understanding of the neural mechanisms that underlie ToM. In addition, new AI algorithms for inferring human mental states have been proposed with more complex applications and better generalisability. In this review, we synthesise the existing understanding of ToM in cognitive and neurosciences and the AI computational models that have been proposed. We focus on preference learning as an area of particular interest and the most recent neurocognitive and computational ToM models. We also discuss the limitations of existing models and hint at potential approaches to allow ToM models to fully express the complexity of the human mind in all its aspects, including values and preferences.

36. Intranasal delivery of siRNA targeting ApoE4 as potential treatment of Alzheimer’s disease

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Keywords: Neurocognition, Neurodegenerative Disorders, RNAi, ApoE4, intranasal delivery, Alzheimer’s disease

Apolipoprotein E (ApoE) has been identified as a critical genetic target in Alzheimer’s disease (AD) with three isoforms, among them ApoE4 demonstrates an elevated disease risk while ApoE2 lowers this risk. ApoE4 plays a pivotal role in the pathogenesis of AD through its metabolic associations with Aβ, tau protein, and neuroinflammation. In this study, an intranasal delivery strategy of nucleic acid therapeutics was employed to design precise targeting of ApoE4 using siRNA along with intranasal delivery formulations involving lipid nanoparticles (LNPs) and polymers, which could help biologics bypass the blood brain barrier (BBB) and translocate into the brain. siRNA targeting total ApoE formulation was prepared as model and control, and characterized, including particle size, zeta-potential and TEM imaging following the permeability assessments of siRNA-loaded formulations on an in vitro nasal mucosa model. Additionally, siRNAs specifically targeting ApoE4 were designed and their ability to target and degrade ApoE4 mRNA was tested using qPCR in both normal H4 cells and ApoE4 knock-in H4 cells. Effective siRNA that downregulates ApoE4 expression were identified. These findings indicate the therapeutic potential of ApoE4-targeting siRNA, and formulations with ApoE4-targeting siRNA will be further evaluated in subsequent experiments by intranasal administration to human ApoE4 knock-in mice to assess its disease-modifying effects in AD animal models, including its interactions with Aβ and Tau proteins.
Cannabidiol exhibits therapeutic potential in vitro for Alzheimer’s disease

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Keywords: Neuropharmacology, Neurodegenerative Disorders

Alzheimer’s Disease (AD) is a progressive neurodegenerative disease marked by deficits in memory and learning skills. It is characterized by the deposition of amyloid beta and tau hyperphosphorylation as well as neuroinflammation. Although current treatments can provide symptomatic relief for AD patients, there is still a need to develop new and more effective therapeutics. Recent Studies have shown that the cannabinoid cannabidiol (CBD) has a wide range of biological effects, including neuroprotective, anti-inflammatory, and antioxidant capabilities. It is therefore being researched as a possible multifunctional AD therapy approach. This study aims to investigate in vitro therapeutic potential of CBD in established pharmacological cellular models for AD. Firstly, MTT assay was used to evaluate the neuroprotective action of CBD on β-amyloid (Aβ)-induced neurotoxicity in neuronal SH-SYSY cells. The thioflavin-T assay was further used to test the effect of CBD on amyloid self-aggregated aggregation. The effect of CBD on glyceraldehyde-dehydro- induced tau phosphorylation was also evaluated by ELISA kits. In addition, the anti-inflammatory effects of CBD on regulation of cGAS-STING signalling against BV-2 microglial cells upon 2′3′-c-cGAMP stimulation were investigated. The results of the study show CBD can modulate amyloid aggregation and tau phosphorylation in SH-SYSY cells. CBD also can regulate inflammatory process via cGAS-STING signalling in BV-2 microglial cells. Overall, CBD presents its excellent functionality as an anti-AD agent. Given that CBD lacks psychoactivity, it may represent a novel therapeutic potential for this neurological disorder.

Renin-induced microglial proinflammatory response enhances dopaminergic neuronal death

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Keywords: Neurodegenerative Disorders, (Pro)Renin receptor, microglia, Rho Kinase protein

Renin angiotensin system regulates the inflammatory microglial responses. In the brain, renin, its precursor (pro)renin, and prorenin receptors (PRR) have been the least studied components. However, in previous studies, we have demonstrated the presence of PRR in glial cells and neurons in the nigrostriatal system of rodents and primates, including humans. In this study, we investigated the role of PRR in the microglial inflammatory response, in vitro using the murine microglial line BV2 as well as primary rat microglia and in vivo using rat and mouse animal models. PRR were upregulated in the nigral region, mainly in microglia, during the neuroinflammatory response. Furthermore, treatment of microglial cells with (pro)renin induced the expression of microglial proinflammatory markers, which we observed to be mediated by increased NADPH-oxidase and Rho-kinase activities, as well as down-regulation of autophagy and up-regulation of inflammasome activity. Interestingly, we have shown that a conditioned medium of (pro)renin-treated microglia exacerbates the death of dopaminergic neurons compared with the medium of untreated microglia. However, the effect of (pro)renin on microglial cells and on the death of dopaminergic neurons was blocked by pretreating microglia with fasudil, a Rho-protein kinase inhibitor, revealing the important role of Rho-kinase activation in the proinflammatory effects of (pro)renin on microglia. To conclude, activation of microglial PRR enhances the microglial pro-inflammatory response, and deleterious effects of microglia on dopaminergic cells, and microglial NADPH-oxidase, Rho-Kinase, and autophagy are involved in this process.

Investigating ApoE4-mediated molecular mechanism of H4 neuroglioma cells of Alzheimer’s disease

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Keywords: Metabolomics, Proteomics, Alzheimer’s disease, ApoE4

Apolipoprotein E4 (ApoE4) is the significant risk gene for late-onset Alzheimer’s disease (AD), which is not only associated with the AD pathological features including amyloid-β deposition, phosphorylation of tau proteins and neuroinflammation but also involved with metabolism, neuron growth, and synaptic plasticity. The aim of this study is to investigate the potential mechanism of the risk gene ApoE4 involved in AD based on the metabolites and protein levels in ApoE4-carried H4 neuroglioma cells. This study presents a novel workflow for AD metabolomics that uses Orbitrap trapping secondary ion mass spectrometry (OrbiSIMS) as a screening tool to gain a non-biased overview of metabolic alteration under ApoE4-carried neuroglioma cells. This approach enabled the detection of 192 putatively annotated metabolites in our study. The higher percentage of lipids detected by OrbiSIMS in negative ion mode makes us identify that glycerophospholipid and sphingolipids metabolism was inhibited by ApoE4. The alanine, aspartate, and glutamate metabolism pathways were also found affected by ApoE4. To validate this, polar-targeted metabolomics of LC-MS was applied to exploit these polar compounds in more detail, which revealed that the metabolism of taurine and hypotaurine is also affected by ApoE4. To validate this, polar-targeted metabolomics of LC-MS was applied to exploit these polar compounds in more detail, which revealed that the metabolism of taurine and hypotaurine is also affected by ApoE4. In addition, to investigate the role of ApoE4 in protein level, proteomics was analyzed on the Vanquish™ Neo UHPLC System coupled with Orbitrap Eclipse mass spectrometer, and finally, 2925 proteins were obtained. 1503 proteins have been selected by filtering the protein with ApoE4/control ratio of > 2 and < 0.5. Network building was performed using the STRING database by inputting them followed by functional enrichment analysis that suggests a nitrogen compound metabolic process. RNA splicing process and translation have been associated with ApoE4-related AD development.

Predicting outcomes for patients with dementia needing psychiatric inpatient care

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Keywords: Neurodegenerative Disorders, Neuroregeneration, Dementia, Neuropsychiatry

Dementia represents a major health challenge. Patients can develop behavioural and psychological symptoms which require them to be cared for in specialist dementia mental health wards. However, there has been little research on the needs of these patients, their mortality or discharge outcomes, although it is known that the wishes of patients are to be discharged home and not to have any further readmission to a psychiatric ward. The work presented here explores whether patients’ outcomes can be predicted at their time of admission to the ward. If it is possible, it could allow targeted interventions to optimize discharge outcomes. We conducted a retrospective analysis of 576 patients admitted to specialist mental health dementia wards using the electronic patient record from the Cambridgeshire and Peterborough NHS Foundation Trust. We performed a Kaplan-Meier survival analysis to investigate patients’ mortality. Demographic and clinical variables were then used to build machine learning models predictive of specific outcomes (death within a year of admission or not; successful or unsuccessful discharge). We found that the median survival length of patients post-admission is 680 days. We could not build accurate models to predict patients at risk to die within a year of admission. However, we found sufficient differences between patients experiencing other discharge outcomes to build a logistic regression model predicting their likelihood of successful discharge, which we define as going home with no further readmission. The high rate of mortality on wards indicates an enhanced need for palliative care, but any intervention cannot be targeted using the information we examined. However, routinely collected data can be used to build machine learning models with a clinical utility to predict patients likely to experience successful or unsuccessful discharges, opening possibilities for the development of tailored interventions aimed at maximizing discharge home.

41. A Healthy Brain Needs Vitamin-T

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Keywords: Neurocognition, Affective Disorders, Neuropsychiatry - Schizophrenia, Neurodegenerative Disorders, Neuroregeneration, affective touch, stress, dementia.

Chronic stress is the cause of many adverse changes in the brain: increased release of glucocorticoids, widespread inflammation, changes in neuronal morphology such as myelination in prefrontal cortex (PFC) and hippocampus (HC), reduced levels of neurotrophic factors such as Fibroblast Growth Factor2 (FGF-2), alterations in brain connectivity especially within PFC -amygdalo-HPC networks, and circadian disruption. Chronic stress has also been found to be an antecedent of cognitive impairment and dementia. Affiliative tactile interactions are known to buffer social mammals against neurobiological and behavioural effects of stress, and within human populations the recent COVID pandemic, where for the first time in human evolution affective touch was significantly restricted, we saw the adverse consequences on people’s stress levels and subsequent mental health. But what’s the mechanism? Here we will make a case for the role of a relatively recently discovered (in humans) population of cutaneous low threshold mechanosensitive c-fibres called c-low threshold mechanoreceptors (CLTM) as a neurobiological substrate responsible for regulating resilience to stress. C-fibres, as a class of unmyelinated afferents, provide a singular vital function in animals - one of protection. Children born with a congenital absence of c-nociceptors will break a bone and not know it. The CLTM is now being understood to also provide a singular vital protective function, from the nurturing touch of a mother to its absence in loneliness. And now we have evidence of their putative role in dementia and schizophrenia from recent animal studies. A case will be made here for what we are describing, by analogy with the vital role that vitamins play in our physical health, for affective touch as Vitamin-T.

42. Exploring the expression of candidate MS progression genes in human pluripotent stem cell-derived neural models

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Keywords: Neurodegenerative Disorders, Neuroregeneration, Multiple Sclerosis, Progression, GWAS

There is a significant unmet clinical need for treatments that prevent or delay progression in Multiple Sclerosis (MS). As part of the International MS Genetics Consortium, we recently completed a genome-wide association study of disease severity, which identified an intergenic single nucleotide polymorphism (rs10191329) as significantly associated with progression. This SNP lies in a regulatory region (GH02J071448) on chromosome 2, between ZNF638 and DYSF. The proteins encoded by both genes have functions that make them plausible candidates; ZNF638 having important roles in viral silencing and DYSF being involved in plasma membrane repair. Single cell transcriptomic analysis has confirmed that both genes are expressed in the central nervous system (CNS), particularly in oligodendrocytes and neurons. However, their subcellular localisation and function in the CNS remain unclear. Our primary aim is to more clearly define the cell-type specific expression of ZNF638 and DYSF in the CNS. We are using a combination of in silico analysis of existing single cell RNA sequencing (scRNA-seq) atlases from human cerebral organoids together with immunofluorescence staining and western blotting of human pluripotent stem cell (hPSC)-derived neuronal progenitor cells, neurons, and cerebral organoid slice cultures to assess ZNF638 and DYSF in CNS tissue at the protein level. Existing scRNA-seq data from cerebral organoids reveals that ZNF638 and DYSF differ greatly in expression during organoid development. We will next extend this analysis to hPSC-derived oligodendrocyte progenitor cells, oligodendrocytes, and neurons. In future we will establish isogenic cell lines based on the rs10191329 variant to explore the impact of the progression-associated allele. Such work will shed light on the molecular mechanisms underlying the association between this SNP and MS progression, thereby revealing targets for drug development.
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Keywords: Neuroregeneration, OPC, NMMA, Remyelination

Remyelination is a process that involves the regeneration of myelin sheaths around nerve fibers. This process is critical for maintaining the proper function of neural tissues and is essential for repairing damage caused by diseases such as multiple sclerosis. However, remyelination is a complex and poorly understood process, and there is a need for new technologies to better understand and improve this process.

The device integrates soft, flexible electrodes using PDMS and PEDOT:PSS layers. Its flexibility and stretchability enable effective spatial and temporal monitoring of the gut-brain axis, offering insights into disorders like irritable bowel syndrome and gastroparesis.

Endoplasmic reticulum luminal content dynamics in neurons

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Keywords: New Technologies, Neurodegenerative Disorders, Single-particle tracking, endoplasmic reticulum, calcium

In neurons, the Endoplasmic Reticulum (ER) forms an extensive network of thin tubes interconnected with junctions, extending from the soma to both dendrite and axon terminals. For healthy neurons, the ER lumen is mostly continuous throughout the entire network ensuring transport and homogenisation of its content. Some forms of Hereditary Spastic Paraplegia have been associated with mutations in ER-shaping proteins, and although mechanistic explanations are still missing, it indicates that maintenance of ER shape is important for neuronal health. A relevant role for the ER in neurons is its function as a calcium store allowing its timely intake and release from and to the cytosol. I will present our investigation of the dynamics of the ER luminal content through super-resolution single-particle tracking microscopy of a small inert luminal ER probe in live human neurons derived from induced pluripotent stem-cells. By imaging single-molecules at very low-density and following the spots in time, we reconstruct trajectories of individual molecules moving inside the ER lumen that we use to extract parameters of the motion. Our results suggest that the dynamics in the long tubules of neuronal projections is different than in monkey kidney cells - COS7, a reference cell line for studying peripheral ER as well as in mouse astrocytes.

46. Digging deeper into pain

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Keywords: Behaviour, Ethology, Nociception, Inflammation, Arthritis, Collitis

The pressing need for safer, more efficacious analgesics is felt worldwide. Pre-clinical tests in animal models of painful conditions, represent one of the earliest checkpoints novel therapeutics must negotiate before consideration for human use. Traditionally, the pain status of laboratory animals has been inferred from nociceptive
assays, measuring their responses to noxious stimuli. The disconnect between how pain is tested in laboratory animals and how it is experienced by humans may in part explain the shortcomings of current pain medications and highlights a need for refinement. We surveyed human chronic pain patients who assert that everyday aspects of life, such as cleaning and leaving the house, are affected by their on-going level of pain. Accordingly, we tested the impact of painful conditions on an ethological behaviour of mice, digging. Stable digging behaviour was observed over time in naive mice of both sexes. By contrast, deficits in digging were seen following acute knee inflammation. In the monosodium iodoacetate knee osteoarthritis model, the decrease in digging observed was not fully ameliorated by a clinically used drug, which reflected the opinion of human patients regarding its effectiveness. Lastly, in a visceral pain model, the decrease in digging behaviour correlated with the extent of disease. Ultimately, we make a case for adopting ethological assays, such as digging, in studies of pain in laboratory animals, which we believe to be more representative of the human experience of pain.

47. Probing the habitual basis of dysfunctional checking in a rodent analogue of compulsive-like checking in obsessive-compulsive disorder

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Keywords: Neuropharmacology, Neuropsychiatry - Addiction, Obsessive-compulsive disorder, Reward, Dopamine, Compulsivity, Learning

Background. Excessive and maladaptive checking is a major subtype of obsessive-compulsive disorder and can be modelled in humans and rats using the Observing Response Task, distinguishing between functional and dysfunctional checking. This study sought to formally test whether dysfunctional checking is habitual. Methods. Twenty-four male Lister Hooded rats underwent discrimination training wherein a cue light indicated which of two levers was currently reinforced to earn a reward, with the correct lever changing throughout each session. Given previous reports of elevated levels of dysfunctional checking in sign-tracking rats, rats were separately phenotyped as goal-trackers (GT), sign-trackers (ST), and intermediates on a Pavlovian autoshaping task. The habitual basis of checking in terms of functional (OLPs) and extra observing lever presses (eOLPs) was tested with two different probes in which the contingency between checking and cue light was degraded, using an extinction probe and an uninformative cue. With ST thought to rely more on model-free learning, it was predicted that dysfunctional checking in ST, unlike GT, would be insensitive to contingency degradation. Results. Comparing baseline and degraded OLPs in ST suggests habitual checking for both probes. While eOLPs in ST significantly decreased upon uninformative cue presentation, negating habitual checking, their dysfunctional eOLPs significantly increased following extinction, potentially modulated by greater uncertainty.

48. Mesenchymal stem cell (MSC)-derived extracellular vesicle (EV) regulation of sensory neuron functions

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Keywords: Neuropharmacology, Neuropsychiatry - Addiction, Obsessive-compulsive disorder, Reward, Dopamine, Compulsivity, Learning

Mesenchymal stem cells (MSCs) are promising therapeutic agents in treating different conditions, including osteoarthritis (OA). Moreover, recent investigations have underscored the pivotal role played by MSC-derived extracellular vesicles (EVs) that enable biomolecular cargo exchange between cells. We recently demonstrated the capacity of MSC-EVs to alleviate OA pain in a mouse model, which was due to MSC-EV amelioration of OA-induced sensory neuron hyperexcitability, rather than modifying joint pathology, thereby illuminating their potential in pain management. Notably, in vitro experimentation spotlighted MSC-EVs’ direct influence on sensory neuron function, reversing nerve growth factor (NGF)-induced nociceptor sensitization (NGF plays a key role in OA pain pathology). However, the underlying mechanisms orchestrating MSC-EV-mediated regulation of sensory neuron activity remain elusive. In this study, using the NGF dorsal root ganglia (DRG) neuron sensitization model, neurons were treated with human bone marrow-derived MSC-EVs and neuron excitability was evaluated using whole-cell patch-clamp electrophysiology. Patch clamp was performed on isolectin B4 (IB4) negative neurons, those most likely to express the NGF receptor - tropomyosin receptor kinase A (TrkA). When MSC-EVs were ‘shaved’ with either trypsin or protein kinase A, a reduction in MSC-EV modulation of neuronal activity was observed. This suggests that interactions between MSC-EV extravesicular proteins and DRG neurons are required for DRG regulation to occur, perhaps involving MSC-EV internalization. Further research is required to fully elucidate the mechanisms by which MSC-EVs regulate DRG neuron function and thus determine their potential for refining pain management.

49. Genes and Cognition study, a recallable cohort to study Dementia or Alzheimer’s disease

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Keywords: Neurocognition, Neurodegenerative Disorders, Cognition, Polygenic risk score, Alzheimer’s disease

Background: Decades of research have not resulted in a cure for dementia/Alzheimer’s disease (AD). Most treatments have failed to benefit patients in clinical trials, potentially due to treatment being provided too late when brain damage is irreversible. There is an urgent need to understand the disease mechanism at the preclinical and prodromal stages of AD, which requires early identification of participants at risk of AD. Method: We attempt to address this need by establishing an open cohort named Genes and Cognition (GC), nested within NIHR Bioresource and comprising 21,051 healthy people aged 17-85 who consented to be recalled for follow-up studies. Participants took 11 cognitive tests (CTs) covering various domains of cognition, in addition. AD polygenic risk (high vs low) was determined in 10,038 participants using 20 single nucleotide polymorphisms (SNPs) from Lambert et al. (PMID:24122737) to identify the earliest age with a noticeable score difference in CTs. Result: CT scores (higher score indicates poorer
performance) were associated with age and gender differences were significant for each CT score. Significant linear trends were observed between CTs and educational attainment. We observed that three CTs (Reaction Time, Stroop Box, Stroop Ink) began deviating around age 55 between high (≥ 96th percentile) and low (≤ 95th percentile) AD polygenic risk groups, although not significant. Similar deviations in some CTs were observed among APOE E4 allele carriers compared to E3/E3 carriers. However, AD risk groups determined without including the APOE region indicated such deviation after age 65.

50. **A systematic investigation of social-semantic knowledge in frontotemporal dementia syndromes and unilateral anterior temporal lobectomy**

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Keywords: Neurocognition, Neurodegenerative Disorders, Neuropsychology, frontotemporal dementia

Degraded semantic memory is a key feature of frontotemporal dementia (FTD). The degree to which social-semantic knowledge is (i) impaired by FTD, (ii) supported across the left and right anterior temporal lobes (ATLs), and (iii) distinct from conceptual knowledge more generally, is unclear. We developed a battery of tests assessing knowledge of multiple, different types of social concept. Performance was directly compared with general conceptual knowledge. Forty-eight people with FTD (behavioural-variant FTD=26; semantic dementia =22) and 19 age-matched healthy controls were recruited. In addition, eighteen people with unilateral anterior temporal lobectomy for temporal lobe epilepsy (left TLE=11, right TLE=7) took part. Participants completed both test batteries, and a subset had a 3T T1-weighted structural MRI scan. Principal component analysis (PCA) was conducted on all tasks in the FTD cohort to determine the underlying neuropsychological dimensions in the data and voxel-based morphometry (VBM) was used to explore grey matter differences between groups. Multiple regression models were built to determine the contributions of (i) magnitude and (ii) asymmetry of ATL and orbitofrontal cortex volume to social-semantic performance. People with FTD were impaired across all social- and non-social semantic tasks. Mild impairments were found after unilateral ATL resection, with no significant left versus right differences. The PCA extracted three components: FTD severity, semantic knowledge, and executive function. Social and non-social semantic tasks co-loaded on to the semantic knowledge component. Factor scores correlated bilateral ATL volume and were significantly predicted by total ATL volume ($t=7.82$, $p<0.0001$), but not ATL asymmetry ($t=0.29$, $p=0.78$). Based on these findings, we propose that social-semantic knowledge represents part of a broader semantic system, supported by a functionally singular semantic hub and interaction with modality-specific spokes.

51. **Characterizing autophagy impaired Schwann cells in Krabbe model affecting neurodegeneration and neuro inflammation.**

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Keywords: Neurodegenerative Disorders, Krabbe disease, Schwann cells, Myelin, Macrophage, Autophagy.

Krabbe’s disease (KD) is a lysosomal storage disorder caused by a deficiency of galactosylceramidase (GALC) resulting in extensive demyelination, neurodegeneration, and neuroinflammation in the central and the peripheral nervous systems. An ongoing study in our lab shows that autophagy, a major mechanism for degrading intracellular macromolecules, is impaired in KD during disease initiation and progression which likely contributes to disease pathogenesis and severity. In Schwann cells (SCs), autophagy is crucial for myelin debris degradation and clearance. To study the role of autophagy during disease initiation and progression, we deleted Atg7, regulator of canonical autophagy, in our Schwann cell-specific KD model. We are currently evaluating the consequences. So far, we have observed that deleting Atg7 in SCs slightly worsens myelin abnormalities and myelin thickness along with physiological tests such as rotarod and electrophysiology. In addition to the observed myelin phenotype, we would like to evaluate whether deleting Atg7 also affects neurodegeneration and neuroinflammation aspects of the disease. We plan to analyze these aspects by quantifying smethion and EM images of sciatic nerve cross sections. By evaluating the role of autophagy in KD, we aim to determine whether enhancing autophagy pharmacologically could be beneficial in treating the disease. Furthermore, this research could also offer valuable insights into novel therapeutic strategies for treating other lysosomal and autophagy disorders.

52. **Circadian clocks in human cerebral organoids**

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Keywords: New Technologies, Neurodegenerative Disorders, Neuroregeneration, brain, organoid, human, circadian, glucocorticoid, clock, rhythm, temperature

Circadian rhythms result from cell-intrinsic timing mechanisms that impact human health and disease. To date, however, neural circadian research has largely focused on the hypothalamic suprachiasmatic nuclei (SCN) of nocturnal rodents. Whether circadian rhythms exist in human brain cells is unknown. Here we show bona fide circadian rhythms in cultured human neurons, glia, and cerebral organoids [1]. The period length of these rhythms is compensated across the range of normal human brain temperatures [2]. Notably, we find circadian rhythmic PER2 translation to be more robust than transcriptional rhythms in Bmall. Human neural circadian rhythms are synchronised by physiological systemic timing cues such as glucocorticoids and daily temperature cycles [2]. In cerebral organoids, rhythmic responses to glucocorticoids recapitulate key
neurodevelopmental transitions in mineralocorticoid and glucocorticoid receptor activation [3-7]. Finally, we observe circadian variation in electrical activity in neural cultures and demonstrate that brain-permeant drugs can modulate circadian clocks in human brain organoids. Our results establish that human brain cells and tissues can sustain their own circadian oscillations and suggest that the canonical model of the molecular circadian clockwork is inadequate to fully explain these rhythmic phenomena. 2D and 3D human neural cultures represent complementary and tractable models for exploring the development, disruption, and mechanics of the daily clockwork within human brain cells, with important implications for chronobiology, brain function, and brain health.

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53. Lymphocytes are recruited to the CNS in patients with Parkinson’s disease (PD) and cognitive impairment

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Keywords: Neurocognition, Neurodegenerative Disorders, Neuroinflammation

Previous studies in PD suggest a decrease in circulating lymphocytes. We hypothesised that this may be due to a shift from the peripheral circulation into the central nervous system and that this shift may be greater in those patients who go on to develop cognitive impairment. We were also interested in CSF IgA positive B cells which have been described in the meninges in mice and humans. They are traditionally associated with mucosal immunity but are now also known to be ‘trained’ following exposure in the gut to pathogens (then homing to the meninges to protect the brain). We used a 15-colour flow cytometry panel on peripheral blood mononuclear cells and CSF-derived immune cells obtained at baseline from 40 newly-diagnosed PD cases and 40 healthy controls. Patients were stratified by the presence of cognitive impairment at 3 years (defined by an ACE-III below 89 at follow up). We used the CSF: blood ratio at baseline as a measure of the shift in cell populations from the periphery to the CNS. We found an increased CSF: blood ratio of CD19+ B cells (p=0.03), CD8+ T cells (p=0.002) and IgA positive B cells (p=0.006) in PD patients with cognitive impairment at 3 years versus controls. IgA positive B cells were found almost exclusively in the CSF of patients with cognitive impairment. IgA positive B cells and CD19+ B cells proportions and counts were similar across the groups in the blood. The CD4:CD8 ratio was also increased in the blood in the cognitive impairment group (p = 0.006). Lymphocytes shift from the periphery to the CNS in Parkinson’s disease. This shift is associated with the development of cognitive impairment. The presence of IgA positive B cells in the CSF is intriguing and merits further exploration as one of the mechanisms linking the gut and the brain in Parkinson’s disease. Therapeutic strategies reducing the recruitment of lymphocytes to the CNS warrant exploration in early PD.

54. Gene delivery of nucleic acid therapy targeting MART for the treatment of Alzheimer’s disease

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Keywords: Neurocognition, Neurodegenerative Disorders, MAPT, RNAi, Alzheimer’s disease

Alzheimer’s disease (AD) is a progressive neurodegenerative disease that affects thousand million of people worldwide. Despite the earlier development of the therapeutic drugs on the market, the current treatment options for AD remain severely limited. For the AD pathology, in addition to the well-known amyloid-beta (Aβ) forming the plaque, the abnormal accumulation of phosphorylated tau protein is considered another important neuropathologic hallmark of AD. Tau protein is translated and expressed by the microtubule-associated protein tau (MAPT) gene. Therefore, biologics targeting MAPT gene like nucleic acid therapeutics may provide a promising approach to AD treatment. In this study, we firstly set up an in vitro AD cell model before preliminary evaluation of drug effects, secondly design, synthesize and test antisense oligonucleotides (ASOs) of total tau and ptau181 as the target genes to downregulate the expression of the abnormally expressed phosphorylated tau181. Briefly, the cells were differentiated into neuronal cells through treatment with retinoic acid (RA). Furthermore, the SH-SY5Y cells were treated with glyceraldehyde (GA) to induce abundant expression of phosphorylated tau. An AD model was established with increased expression of total tau, Thr 181, Ser 199, and Ser 396 as well as decreased axon length of neuronal cells. Before evaluating the transfection efficiency of ASOs, cellular cytotoxicity of lipofectamine 2000 and ASO tested at the experimental concentrations was investigated and no toxicity was found for both. In the following experiment, the transfection efficiency of ASOs will be examined and reflected by changes in cellular phosphorylated tau levels and the status of neuronal cells differentiated from SH-SY5Y cells.

55. Neuroinflammation is elevated in people with Parkinson’s disease with higher risk of developing dementia: baseline findings from the NET-PDD study

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Keywords: Neurocognition, Neurodegenerative Disorders, Parkinson’s Disease, Dementia, Neuroinflammation, Tau Accumulation

Introduction: The development of dementia is a devastating aspect of Parkinson’s disease (PD), affecting half of patients within 10 years post-diagnosis. To develop effective therapies to prevent/slow progression to PD dementia (PDD), the mechanisms that determine why some people with PD develop early dementia, while others remain cognitively unaffected, need to be understood. Objective: Neuroinflammation and tau are strongly linked to cognitive decline in other neurodegenerative disorders. Both of these have been
have been demonstrated in post-mortem PD brains, suggesting that these processes could mediate dementia risk early-on in the PD disease course. We hypothesised that higher dementia risk patients have greater inflammation and/or tau. Method: The NET-PDD study longitudinally assesses forty newly-diagnosed PD patients and twenty age-matched controls, using [11C]PK11195 PET for microglial activation (indexing neuroinflammation) and [18F]AV1451 PET for tau. Participants are stratified into two groups at low and high dementia risk (pentagon copying, semantic fluency, MAPT genotype). Binding potentials in 46 regions were compared, and associations between tracers tested. Results: We found elevated neuroinflammation in multiple subcortical regions in high dementia risk patients. In low-risk this was much more limited. Regional inflammation was associated with worse cognitive performance (ACE-III) and whole brain inflammation with serum cytokine levels. In contrast, tau PET showed increases restricted to off-target binding regions, no relationship with cognition, but moderate correlation with serum p-tau181. Finally, the degree of neuroinflammation and tau burden correlated positively across all brain regions, with association strength being greatest in high dementia risk. Conclusion: Significant regional neuroinflammation in early PD might underpin higher risk for PDD development - suggesting neuroinflammation as a putative key modifiable disease factor.

56. Epidemiology of syndromes associated with Frontotemporal Lobar Degeneration in the East of England

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Keywords: Neurodegenerative Disorders, Frontotemporal lobar degeneration, FTLD, PSP, CBS, FTD, Epidemiology, Survival

Background: Representative data is critical to understanding presentation, prevalence, and survival in neurodegenerative diseases. Syndromes associated with FTLD are progressive conditions whose epidemiology is poorly understood, and population representative samples are not readily available. We aimed to define the epidemiology of syndromes associated with Frontotemporal Lobar Degeneration. Methods: Data was acquired through the PIPPIN study - an epidemiological, prospective, observational study in Cambridgeshire and Norfolk (population 1.8m), of people with Progressive Supranuclear Palsy and Lewy body disease. Using Flow cytometry, we identified

57. Identifying the neural correlates of cognitive reserve

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Keywords: Neurodegenerative Disorders, Cognitive Reserve

Objective: A direct relationship between neuropathology severity and cognitive decline is not always observed. This discrepancy may be explained by a compensatory mechanism of cognitive reserve. The current study examined whether neural correlates of cognitive reserve can be found. Methods: An EEG study of 38 elderly participants was conducted, involving a sustained attention task under two arousal states: alert and drowsy. Task performance metrics included mean reaction time (RT) and errors. Cognitive reserve was operationally defined by task performance variability between the two arousal states. EEG signal complexity was assessed using the Lempel-Ziv (LZ) algorithm. We explored interactions between arousal, performance, and various brain regions. Additionally, we performed exploratory correlations between cognitive reserve and both structural cortical volume and graph theoretical measures of white matter connectivity. Results: Two-way ANOVAs revealed a significant interaction between arousal and performance for mean RT and omission errors. Three-way ANOVAs found interaction effects between arousal, performance, and ROI for several metrics, most pronounced in frontal areas. Structural volume and connectivity did not consistently correlate with cognitive reserve. Conclusion: Findings show a link between task performance and informational complexity under neurocognitive strain, implying a compensatory mechanism. Yet, no clear relationship was found between structural and connectivity metrics and cognitive reserve. Further studies are required for a more comprehensive understanding.

58. Peripheral innate immunophenotype in neurodegenerative dementias: a transdiagnostic approach

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Keywords: Neurodegenerative Disorders

The number of people living with dementia is predicted to increase to 150 million worldwide by 2050. To improve the clinical understanding and treatment of all-cause dementias one could target disease-specific pathogenic processes. Alternatively, one could target the commonalities, or transdiagnostic pathogenic processes. The innate immune system plays an integral role in the progression of many pathologies of dementia. In addition to central innate immune cells (microglia), peripheral innate immune cells (monocytes, natural killer and dendritic cells) are implicated in neurodegenerative disease. However, current characterization of these cell types across a range of pathologies is incomplete. The present study aims to characterize peripheral innate immunophenotype in 170 patients with Alzheimer’s disease, Frontotemporal Dementia (non-Fluent and semantic variant primary progressive aphasia and behavioral frontotemporal dementia), Corticobasal syndrome, Progressive Supranuclear Palsy, and Lewy bodies disease. Using Flow cytometry, we identified
discrete innate immune cell types to be altered in dementia patients as compared to controls. Further, we present a novel comparison between dissimilarity analyses coupled with dimensionality reduction technique. We have identified innate immune profiles specific to each diagnostic group with a neurodegenerative dementia. In conclusion, conclude that peripheral innate immune cells serve as useful blood biomarkers to aid in clinical diagnosis of dementia, and highlight immunotherapeutic potential for multiple dementias.

59. Genetic risks of Alzheimer’s by APOE and MAPT on cortical morphology in young healthy adults

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Keywords: Neurodegenerative Disorders

Introduction: Genetic risk factors such as APOE ?4 and MAPT i.e., carriers of both risk factors showed increased tau pathways and grey matter changes at both early and established stages of Alzheimer’s disease, but their effects on cortical morphology in young healthy adults remain unclear.

Methods: 144 participants aged from 18 to 24 underwent 3T MRI and genotyping for APOE and MAPT to investigate unique impacts of these genetic risk factors in a cohort without significant comorbid conditions such as metabolic and cardiovascular diseases. We segmented the cerebral cortex into 68 regions and calculated the cortical area, thickness, curvature, and folding index for each region. Then, we trained machine learning models to classify APOE and MAPT genotypes using these morphological features. In addition, we applied a growing hierarchical self-organizing maps algorithm, which clustered the 68 regions into 4 subgroups representing different morphological patterns. Then, we performed general linear model analyses to estimate the interaction between APOE and MAPT on cortical patterns. Results: We found that the classifiers using all cortical features could accurately classify individuals carrying genetic risks of dementia outperforming each individual feature alone. APOE-4 carriers had more convoluted and thinner cortex across the cerebral cortex. A similar pattern was found in MAPT A allele carriers only in the regions that are vulnerable for early tau pathology. With the clustering analysis, we found a synergistic effect between APOE-4 and MAPT A allele i.e., carriers of both risk factors showed the most deviation of cortical pattern from the typical pattern of that cluster. Discussion: Genetic risk factors of dementia by APOE-4 and MAPT i.e., carriers of both risk factors showed the most deviation of cortical pattern from the typical pattern of that cluster. Discussion: Genetic risk factors of dementia by APOE-4 and MAPT i.e., carriers of both risk factors showed the most deviation of cortical pattern from the typical pattern of that cluster.

60. Resilience of functional connectomes in presymptomatic frontotemporal dementia

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Keywords: New Technologies, Neuroregeneration, network integrity, presymptomatic, frontotemporal dementia, tMRI, Connectivity

Introduction: Carriers of frontotemporal dementia-related mutations can maintain cognitive function during the 10-20 years before expected symptom onset, even in the presence of significant progressive atrophy. The integrity of functional organisation during this presymptomatic stage is proposed to determine this functional resilience to the pathology. Methods: We studied 151 symptomatic and 289 presymptomatic FTD-mutation carriers, and 271 family members without mutations. We analysed functional magnetic resonance imaging using novel gradient mapping technique, to quantify the integrity of the functional connectome, within functional ‘communities’ of cortical and subcortical regions. Results: We confirmed a decrease in network integrity in symptomatic carriers compared to non-carriers. However, there was increased...
network integrity for presymptomatic carriers compared to non-carriers. The strongest effects were observed in inferior-frontal cortex, dorsolateral prefrontal cortex, dorsal anterior cingulate cortex, the intraparietal lobule and superior temporal gyrus. This enhancement of functional connectomes in presymptomatic carriers was behaviourally relevant and independent of the severity of brain-wide atrophy. Conclusion: Our findings suggest that resilience to atrophy may arise from enhanced functional connectomes, protecting against clinical conversion in individuals at risk of dementia. This result has implications for the design of presymptomatic disease-modifying therapy trials, using surrogate markers of brain health rather than clinical end points.

61. A multi-site magnetoencephalography resting-state dataset to study dementia: The BioFIND dataset

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Keywords: New Technologies, Neurodegenerative Disorders, Neuroregeneration
Early detection of Alzheimer’s Disease (AD) is vital for developing effective treatments. Neuroimaging can detect early brain changes, such as hippocampal atrophy in Mild Cognitive Impairment (MCI), a prodromal state of AD. Machine learning can utilise the many features from high-dimensional neuroimaging data, but many cases are required. While large, public datasets of MCI/AD exist for Magnetic Resonance Imaging (MRI), eg ‘ADNI’, comparable datasets are lacking for Magnetoencephalography (MEG). MEG offers advantages in its millisecond resolution, potentially revealing physiological changes in brain oscillations and connectivity before structural changes are evident with MRI (and unconfounded by vascular changes in functional MRI). Here we describe the ‘BioFIND’ dataset of 324 individuals, approximately half MCI and half controls, who have at least 2 mins of resting-state MEG, plus a T1 structural MRI, from one of two sites (Cambridge and Madrid). To our knowledge, this is the largest publically available MEG dataset for dementia research, available in BIDS format on DPUK platform: https://portal.dementiasplatform.uk/Apply. Initial analyses using Multi-kernel Learning (MKL) of Support Vector Machines (SVM) show that MEG sensor covariance adds complimentary information for MCI classification beyond grey-matter volume from structural MRI. Future possible analyses include source space, measures of functional connectivity (e.g. amplitude or phase), dynamic as well as static connectivity, more advanced classifiers (e.g. deep learning); future plans include adding new participants from ongoing projects, and follow-up diagnoses and other biomarkers where available.

62. Validating the clinical utility of AI guided tools for early dementia prediction

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Keywords: Neurodegenerative Disorders, Alzheimer’s disease, Machine Learning, Trajectory modelling, Dementia prognosis
Recent advances in machine learning highlight the potential of AI-guided tools for early dementia prediction with major implications for timely clinical management. Yet, we still lack robust tools for predicting neurocognitive decline early in clinical practice. We have developed a predictive prognostic model based on Generalised Matrix Learning Vector Quantisation that combines multimodal biological and cognitive data to predict cognitive decline. Here we test the clinical validity of this model in predicting individualised cognitive trajectories on real-world memory clinic data.

Method: We trained our model to classify sMCI (individuals with stable MCI diagnosis within 3 years; n=290) vs. pMCI (individuals who progressed from MCI to AD within 3 years; n=138). We tested the model on two clinical samples: Quantitative MRI in NHS Memory Clinics (QMIN MC ); N = 281. Memory Ageing & Cognition Centre at NUS (MACC); N = 195. We trained and tested the model with baseline structural MRI (medial temporal grey matter density) and cognitive data (following data harmonization across training and test samples). Using a scalar projection method, we generated a prognostic index that indicates and classifies individuals as Clinically Stable vs. Declining (slowly vs. rapidly).

Results: Our trained model on ADNI data classified sMCI vs. pMCI with 81.07% class-balanced cross-validated accuracy (sensitivity = 81.52%, specificity = 80.63%). For the clinical MACC and QMIN-MC samples, most AD patients were classified as rapidly progressive compared to MCI patients that were mostly classified as stable or slowly progressive. Survival analysis on the MACC sample for which longitudinal assessments (up to 6 years) are available validated the model predictions, showing that patients with higher model-derived prognostic index darte faster. Conclusion: Validating our AI-guided tool for early dementia prediction in real-world patient data provides evidence for its clinical utility.

63. Neuronal activity bidirectionally regulates myelin plasticity

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Keywords: Plasticity, glia, myelin, oligodendrocytes, neuronal activity
Neuronal activity shapes the central nervous system, however the ability of the white matter to plastically adapt to activity changes, is not fully understood. Here, we use DREADDs to manipulate activity within a fully myelinated white matter tract. We manage to describe how bilateral changes in activity can lead to changes in oligodendrocyte numbers, sheath length, number and thickness. Using in silico simulations, we could predict that these changes were sufficient to affect conduction velocity. Indeed, using in vivo electrophysiological recordings, we could confirm that these myelin changes
affected signal arrival to higher brain areas. Overall, our results show that both pre-existing and newly differentiated oligodendrocytes participate in activity-mediated myelin plasticity, leading to alterations in the physiological properties of the visual pathway.

64. **C9orf72-ALS iPSC microglia are pro-inflammatory and toxic to motor neurons via MMP9**

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**Keywords:** Neurodegenerative Disorders, amyotrophic lateral sclerosis, motor neuron disease, C9orf72, induced pluripotent stem cell, microglia, motor neuron, co-culture

Amyotrophic lateral sclerosis (ALS) is the third commonest neurodegenerative disorder, resulting in progressive motor neuron degeneration and paralysis. In patients with a hexanucleotide repeat expansion (HRE) in C9orf72, the commonest genetic mutation associated with ALS, widespread microglial activation correlates with disease progression. In neurons, the HRE in C9orf72 results in toxicity through both loss- and gain-of-function mechanisms. However, the consequence of the C9orf72 HRE for human microglial function, and whether they show a disease associated phenotype, is less clear. Here, we studied C9orf72 HRE mutant microglia using human induced pluripotent stem cell (iPSC)-derived microglia. We differentiated iPSC-derived microglia from three C9orf72-ALS patients, one isogenic and three healthy controls. iPSC-derived microglia displayed microglial morphology and expressed key markers. C9orf72 protein expression was significantly reduced in C9orf72 HRE mutant microglia compared with healthy controls, indicating C9orf72 loss-of-function. In addition, RNA foci and dipeptide repeat proteins were detectable in C9orf72 HRE mutant microglia, demonstrating the presence of gain-of-function products. Transcriptomic analysis revealed enrichment of pathways associated with immune cell activation and cytokine/chemokines in C9orf72 HRE mutant microglia, particularly after pro-inflammatory priming with LPS. Specifically, we identified consistently increased expression and release of matrix metalloproteinase-9 (MMP9) in LPS-primed C9orf72 HRE mutant microglia. In co-culture, LPS-primed C9orf72 HRE mutant microglia induced apoptotic signaling and neurodegeneration in healthy motor neurons, which was ameliorated by concomitant application of an MMP9 inhibitor. These results demonstrate cellular dysfunction of C9orf72 HRE mutant microglia, and a non-cell-autonomous role in driving C9orf72-ALS pathophysiology in motor neurons through MMP9 signalling.

65. **Salivary alpha-synuclein RT-QuIC for the molecular diagnosis of Parkinson’s Disease**

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**Keywords:** alpha-synuclein, Parkinson’s disease

**Background:** Alpha-synuclein (α-syn) is the main component of Lewy bodies, the pathological hallmarks of Parkinson’s Disease (PD). Oligomeric species of α-syn are thought to arise early in the prodromal phase of PD, exerting toxic effects and propagating aggregated α-syn pathology. The possibility of using saliva - an easily accessible biofluid - to detect seeding-competent α-syn oligomers would represent an important advancement to facilitate the early diagnosis and to monitor progression of PD. **Objective:** To determine whether saliva can be used for the detection of seeding competent α-syn oligomers with Real-Time Quaking Induced Conversion (RT-QuIC) Methods: We performed a prospective diagnostic study with the saliva of thirty-seven de novo PD patients and twenty-three age and sex-matched healthy subjects (HS). Salivary samples were used to detect α-syn seeding competent species by RT-QuIC. Results: A total of 60 salivary samples from de novo PD and healthy subjects (HS) were analysed. Salivary RT-QuIC demonstrated a good diagnostic accuracy: sensitivity 83.78% (95% CI: 68.86-92.35); specificity 82.61% (95% CI: 62.86-93.02), with a Likelihood Ratio of 4.818. Hierarchical clustering and linear regression showed a statistically significant correlation between increased disease severity (evaluated with motor and non-motor scores) and a greater response in salivary RT-QuIC assay. Conclusions: We have shown the possibility to use saliva and RT-QuIC to detect the presence of α-syn seeding competent species to discriminate between PD patients and HS. Further investigations in larger cohorts are needed to confirm the application of salivary RT-QuIC for PD diagnosis and for the assessment of disease severity and progression.

66. **Cell patterning via biotin-streptavidin binding for applications in neural tissue engineering**

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**Keywords:** New Technologies, Neuregeneration, Neural tissue engineering, Cell patterning, Scaffold-free biofabrication

Being able to arrange cells spatially in vitro is essential in developing complex neural tissue mimics to study the human nervous system. In tissue engineering, this control over cell attachment is often mediated by coating scaffolds with extracellular matrix (ECM) proteins such as laminin. However, the interactions between ECM and cell surface receptors would inevitably trigger specific intercellular signalling pathways, which could influence cell fate and obscure experimental results. Here, we aim to employ biotin-avidin binding to pattern neural cells. Using Schwann cells and PC-12 cells, we showed that our biotin-avidin system does not impair cell metabolism, as demonstrated by a commercial alarmarBlue assay. Next, PC-12 cells were patterned on glass substrates functionalized with 3-aminopropyltriethoxysilane (APTES) using microcontact printing. We showed that PC-12 cells could align with the stripped streptavidin and laminin micropatterns for 24-48 h. Lastly, we explored the potential
to generate layered heterocellular neural cultures by conjugating Schwann cells and PC-12 cells with biotin and streptavidin. Taken together, our findings demonstrated the flexibility of using biotin-avidin interactions to engineer complex scaffold-free neural constructs to study human neurophysiology and neurological diseases.

67. Genome-wide CRISPR knockout screening to identify key regulators of autophagy in induced pluripotent stem cell derived microglia

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Keywords: Neurodegenerative Disorders, Alzheimer's disease, CRISPR screening, iPSC, microglia, genetics

Background: A whole genome knockout CRISPR screen in human induced pluripotent stem cell (hiPSC) derived microglia was undertaken to identify regulators of autophagy. With the secondary objective to cross reference these genes to Alzheimer's Disease genome wide association studies to provide potential therapeutic targets for drug development. Method: hiPSC derived microglia precursor cells were transduced with the TKOv3 genome-wide CRISPR/Cas9 knockout library and differentiated for two weeks to microglia in our newly developed media. After two weeks hiPSC-microglia were fed dead double GFP/mCherry fluorescent labelled SH-SY5Y cells to act as a phagocytic cargo. Phagocytosis occurred for 6 hours before washing non-phagocytosed cargo and harvesting and fixing the hiPSC-microglia. hiPSC-microglia were sorted into high and low levels of phagocytosis by fluorescent activated cell sorting for single mCherry positive cells. Genomic DNA was extracted from sorted cell populations and sequenced by Illumina Novaseq. Result: Microglia were successfully transduced at a multiplicity of infection at 0.7 to maximize single guide integration. Successful phagocytosis was observed via FACS with over 60% of hiPSC-microglia phagocytosing dead neurons after 6 hours. Four populations of varying levels of phagocytosis were harvested and genomic DNA extracted and sequenced.

Conclusion: We have developed a pipeline for the first successful genome-wide CRISPR knockout screening in hiPSC-microglia and have used this to identify regulators of autophagy.

68. Neural Knitworks Creating Impact - an international, participatory, neuroscience community engagement tool

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Keywords: Public engagement, participation, education, science communication

Neural Knitworks are based on the principle that yarn craft, with its mental challenges, social connection and mindfulness, helps keep our brains and minds sharp, engaged and healthy. Neural Knitworks create hybrid communities stitching and binding together neuroscience research and a wide audience with diverse interests. Audiences have fun as they design their own wooley neurons, or get inspired by our scientifically-informed knitting, crochet or knot patterns; They natter with neuroscientists and teach them a few crafty tricks; Each event contributes to a travelling, giant textile brain exhibition including neurons from the northern and southern hemispheres. Audiences say they increase attention span and test memory function, calm the mind and craft brain health. Participants forge friendships; solve creative and mental challenges; practice mindfulness and relaxation; teach and learn; develop eye-hand coordination and fine motor dexterity. Here, we share evidence of impact and engagement collected from multiple NK activities since the project was founded in 2012.

69. Comprehensive analysis of the genetic and clinical spectra of SETX in amyotrophic lateral sclerosis

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Keywords: Neurodegenerative Disorders, Amyotrophic lateral sclerosis (ALS), Senataxin (SETX), Next-generation sequencing (NGS), ACMG/AMP guidelines, Variant re-classification

SETX mutations were first linked to Amyotrophic lateral sclerosis 4 (ALS4), an autosomal-dominant juvenile ALS. Later, over 100 SETX variants were discovered, however, much more frequently in adult-onset sporadic ALS (SALS) individuals. Yet, pathogenicity of these variants was unclear, and was each predicted by variable criteria, leading to significant discordance among laboratories. Here, we aim to obtain a comprehensive profile of this outstanding gene in ALS, from our Chinese population and other published studies, to add and update variant data. First, SETX variants were screened by targeted NGS in a Chinese ALS cohort of 496 patients (38 FALS and 458 SALS) and 460 matched controls. We applied a semi-automatic classify system based on refined ACMG/AMP guidelines to categorize and re-categorize all the SETX variants detected here and in published literature. Besides, the clinical manifestations were analyzed to discuss the genotype-phenotype correlation between SETX and ALS. 28 nonsynonymous SETX variants were detected in 6.45% (32/496) of our ALS group, more commonly seen in SALS than in FALS patients. Among the 32 SETX variant carriers, only 2 SALS individuals met criteria for juvenile ALS, most cases displayed features resembling classical ALS rather than ALS4. Interestingly, patients with SETX variants were even prone to bulbar onset, which was opposite to the sparing of bulbar involvement as observed in ALS4. In addition, other 116 variants from literature were collected and re-classified, revealing a proportion of discordance with that predicted by InterVar or documented in ClinVar database. We here present a comprehensive genetic and clinical characterization of SETX gene in ALS, which is of importance for clinical genetic counselling and future gene-specific therapeutic interventions. Novel and rare variants identified here represent important starting points for future research, although their pathogenicity must await further elucidation.
Oligodendrocyte Dynamics Throughout Life

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Keywords: Myelin, Oligodendrocytes, Oligodendrogenesis, Brain regions

The post-acute sequelae of COVID-19, or Long COVID, has widespread and long-lasting multisystemic impacts on patients’ body, cognition and daily functioning, including the ability to work. This has become a far-reaching social problem. Longitudinal studies are important in investigating the expected timelines along the course of recovery. This study adopts a mixed cross-sectional/longitudinal design to examine how symptoms (cognitive and non-cognitive) and objective cognitive function evolve over time in post-COVID-19 patients [n = 187] compared to controls without infection history [n = 207]. Participants completed a questionnaire about their COVID-19 experience and cognitive tasks assessing memory, language and executive function at baseline. They were followed up for approximately 9 months, during which they completed the measures again at 2-3 follow-ups depending on their group. We found varying profiles for different symptoms. While there were improvements over time in some non-cognitive symptoms in post-COVID-19 patients (e.g. gastrointestinal/autoimmune/ fatigue and mood symptoms), cognitive symptoms and neurological symptoms remained unimproved across time. Objective assessments showed persistent impairments in memory function, including response accuracy and speed. Our finding suggested that people with past COVID-19 infection did not experience improvement in cognitive function over time, at least for the duration of this 9-month longitudinal study.


Presenting author: Miss Beiyu Zhang (beiyu.zhang@nottingham.ac.uk)

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Keywords: Neurodegenerative Disorders, Gene therapy, splice-switching antisense oligonucleotides (SSOs), GAG-binding enhanced transduction (GET*), Alzheimer’s disease (AD)

Alzheimer’s disease (AD) is a global health crisis mainly characterized by the aggregation of Amyloid β peptide (Aβ) fragments outside neurons in the brain, forming plaques. The generation of Aβ is mediated by the proteolytic processing of amyloid precursor protein (APP) by β- and γ-secretases. Oligonucleotide treatments, particularly splice-switching antisense oligonucleotides (SSOs), have gained interest for AD therapy. SSOs cause APP exon 17 splicing to promote the production of APP lacking exon 17 to decrease the generation of Aβ. Cell-Penetrating Peptides (CPPs), such as GAG-binding enhanced transduction (GET*) developed by our group, offer efficient and safe cell entry capabilities. In this study, we investigated the loading of designed SSO into SH-SY5Y cells using lipofectamine 2000 and GET* as carriers. The efficacy of SSO through these two carriers in targeting and splicing the APP gene was investigated by using PCR, along with the transfection efficiency of SSO by using human APP protein ELISA assay. Additionally, TEM imaging was employed to examine the structure of SSO-GET* nanoparticles. Overall, our findings demonstrate the effective targeting of the APP gene by SSO. Furthermore, GET* exhibits lower cytotoxicity to transfect SSO into SH-SY5Y cells compared to lipofectamine 2000. PCR analysis confirms the successful delivery of SSO by both GET* and lipofectamine 2000, resulting in the skipping exon of the APP gene and a subsequent decrease in APP protein levels. These findings support the optimization of SSO transfection by focusing on gene therapy targeting APP processing in future work.
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