The 14th UK-KOREA

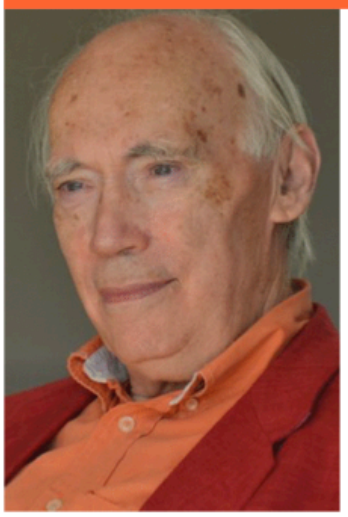
NEUROSCIENCE SYMPOSIUM

15 - 16th August, 2023 (9 am - 5 pm)

Talk Concert:
50 Years of Long-Term Potentiation

MAGDALEN COLLEGE, OXFORD

15th August, 2023 (5pm)



Prof. Tim Bliss

Prof. John O'Keefe

Prof. Graham Collingridge

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15-16th Aug-2023	The 14th UK-Korea Neuroscience Symposium	Magdalen College, Oxford

14th August		Symposium General Enuiry Contact Point; spencer@spencerdouglas.co.uk
15:00-19:00	Arrival/check-in accommodation	Magdalen College, Oxford, OX1 4AU, UK
	Arrival/check-in accommodation	Lincoln College, Oxford, OX1 3DR, UK

15th August

8:45-9:15	Registration (Grove Auditorium, Magdalen College, Oxford)	
9:15-9:20	Opening	
9:20-11:20	**Theme 1 - Aging and Neurodegenerative diseases**	(20min talk + 5 min discussion)
9:20-9:45	**Peter Giese** (King's College London)	Memory mechanisms in the aged and Alzheimer's disease brain
9:45-10:10	**Mi Jin Yun** (Yonsei University, Severance Hospital)	Visualizing reactive astrocyte-neuron interaction in Alzheimer's disease using 11C-acetate and 18F-FDG PET/CT
10:10-10:35	**Maria Spillantini** (Univ. of Cambridge)	Glial cell involvement in the neurodegenerative process in tauopathies
10.35-10:55	**Coffee/Tea break**	Grove Auditorium, Magdalen College
10:55-11:20	**Su Hyeon Son** (Korea Brain Research Institute)	Pathological effect of aggregation protein on the blood-brain barrier in neurodegenerative disease
11:20-11:45	**Tim Viney** (Univ. of Oxford)	Glutamatergic drivers of Tau pathology in the human thalamus
	Last Year Poster Prize Talk	(20min talk + 5 min discussion)
11:45-12:10	Last year UK-Poster Prize Talk: **Shiden Solomon** (King's College London)	The role of AD protective variant PLCγ2-P522R in modulating microglia mediated clearance and synaptic pruning.
12:10-13:30	**Lunch & Poster Session**	Grove Auditorium, Magdalen College
13:30-13:55	Last year Korea-Poster Prize Talk: **Yeon Ha Ju** (Korea Institute of Science and Technology)	Astrocytic urea cycle detoxifies Aβ-derived ammonia while impairing memory in Alzheimer's disease
13:55-16:20	**Theme 2 - Plasticity**	(20min talk + 5 min discussion)
13:55-14:20	**C. Justin Lee** (Institute for Basic Science)	Astrocytic metabolic plasticity
14:20-14:45	**Malte Kaller** (Univ. of Oxford)	Myelin plasticity in the adult brain: How, when, and why?
14:45-15:10	**Peter Kind** (Univ. of Edinburgh)	Understanding cellular and circuit basis of monogenic forms of neurodegenerative disorders.
15:10-15:30	**Coffee/Tea break & Poster Session**	Grove Auditorium, Magdalen College
15:30-15:55	**Ain Chung** (Korea Advanced Institute of Science and Technology)	Neurobiology of Learning to Learn
15:55-16:20	**Cezar Tigaret** (Univ. of Cardiff)	Psychiatric risk from a calcium channel gene: when synaptic plasticity goes wrong.
	Break	

17:00-17:40	**Special Session "50 Years of Long-Term Potentiation (LTP) " with Tim Bliss, John O'Keefe and Graham Collingridge**	
	Talk Concert with audience	Tim Bliss (CRICK), John O'Keefe (UCL), Graham Collingridge (Toronto), Nigel Emptage (Oxford), Frances Edwards (UCL), Kei Cho (KCL)
17:40-18:30	**Pre-dinner drink and LTP 50 reception**	Magdalen College
18:30-21:00	**Formal Symposium Dinner**	Dining Hall, Magdalen College

16th August

	Plenary Lecture	40 min talk + 5 min Q&A
9:00-9:45	**Graham Collingridge (Univ. of Toronto)**	**NMDA receptors and LTP in the hippocampus**
9:45-12:35	**Theme 3 - Circuitry/Computation**	(20min talk + 5 min discussion)
9:45-10:10	**Athena Akrami** (University College London)	TBC
10:10-10:35	**Alan Jung Park** (Seoul National Univ.)	Brain theta state: biomarker for cognitive performance
10:35-10:55	**Coffee/Tea break**	Grove Auditorium, Magdalen College
10:55-11:20	**Taegon Kim** (Korea Institute of Science and Technology)	Input-dependent micromodules in the cerebellar input layer : anatomical detection and computational modeling of the emergent process
11:20-11:45	**Zoltan Molnar** (Univ. of Oxford)	Cortical layer with no known function
11:45-12:10	**Jeongjin Kim** (Korea Institute of Science and Technology)	Neural representation of cognitive-motor integration in basal ganglia outputs
12:10-12:35	**Jaekyeong Kim** (Korea Advanced Institute of Science and Technology)	Roles of sleep oscillations in motor memory consolidation
12:35-13:35	**Lunch**	Grove Auditorium, Magdalen College
13:35-15:40	**Theme 4 - Novel Methods**	(20min talk + 5 min discussion)
13:35-14:00	**Selina Wray** (University College London)	Human stem cells models of familial Alzheimer's disease and familial British dementia
14:00-14:25	**Sangkyu Lee** (Institute for Basic Science)	Sculpting neural circuits via designed neuro-glia interaction
14:25-14:50	**Anna Mallach** (UK-Dementia Research Institute, UCL)	Exploring different plaque environments in Alzheimer's disease using spatial transcriptomics
14:50-15:10	**Coffee/Tea break**	Grove Auditorium, Magdalen College
15:10-15:35	**Youngbin Tchoe** (Ulsan National Institute of Science and Technology)	Neural Interface Technologies for High Resolution Intraoperative Brain Mapping
15:35-16:00	**Maike Lenz** (Univ. of Oxford)	Multimode Optical Fibres as Flexible Hair-Thin Endoscopes for High Resolution Deep Neuroimaging'
16:00-16:25	**Beomsue Kim** (Korea Brain Research Institute)	Tracking microglia and immune cells with a fluorescent small molecule

16:25-16:30	**Closing Remarks**	
	Free Time	
17:15-18:00	**Farewell symposium drink**	Magdalen College
18:00-20:00	**College style buffet dinner**	Dining Hall, Magdalen College

17th August		
9am-12 midday	**Visit in Oxford; event to be confirmed**	Contact to **Dr Haram Park** (Univ. Oxford): haram.park@dpag.ox.ac.uk

Programme Committee

Professor Frances Edwards (University College London)
Professor Nigel Emptage (Univ. of Oxford)
Professor Kei Cho (King's College London)
Professor Eunjoon Kim (IBS-KAIST, Korea)
Professor Uhtaek Oh (KIST, Korea)
Dr Do-Geun Kim (KBRI, Korea)

Local Organisers

Dr. Haram Park (Magdalen College, Univ. of Oxford)
Dr. Fanbo Kong (King's College London)
Mr. Spencer Kong (Spencer & Douglas)

Grove Auditorium

Magdalen Grove Auditorium, opened in 1999 and designed by architect Dr Demetri Porphyrios as part of a new quadrangle for Magdalen College, is of a 'classico-vernacular' design combining Greek Classical form and proportion but using other details and references to give it a timeless appearance.

The Auditorium itself is fully air-conditioned, with tiered seating for 160, and dedicated projection and sound rooms. Each seat is equipped with a pull-out writing 'tablet' to support note-taking. The proscenium arch style stage is on a level with the front row of seating. Considerable attention has been paid to the acoustic standards of the Auditorium and voice amplification is only needed for special circumstances, for example, to provide induction loop amplification for those equipped with an appropriate hearing aid. A Steinway B grand piano is located in a small wing to one side of the stage and is available for concerts. The projection room is equipped not only with the ubiquitous data projector, DVD player and sound system, but also 35mm and 16mm reel-to-reel cinema projectors, inherited from the Barbican Centre, offering a unique film experience.

Magdalen College
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MEMORY MECHANISMS IN THE AGED AND ALZHEIMER'S DISEASE BRAIN

Peter Giese

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Theme 1 - Aging and Neurodegenerative diseases

Learning and memory abilities decline with normal ageing. Alzheimer's disease (AD) exacerbates these impairments, resulting in substantial memory loss. Our research is aimed at developing a mechanistic understanding of these memory impairments. The first part of this talk will address memory formation in aged brain, despite substantial LTP impairment. As suggested by previous work with alphaCaMKII autophosphorylation-deficient mice, we found that aged mice form contextual memory due to generation of multi-innervated spines (MIS) in hippocampus. As MIS are typically 2:1 synapses, their generation changes connectivity between 3 neurons. Thus, the synaptic basis of memory changes with normal ageing. Further, retrieval-induced memory updating is impaired in aged brain, possibly due to MIS generation. The second part of this talk will address how in AD synapses degenerate and cause memory loss. Ultrastructural analysis in human post-mortem brain has shown that MIS density increases in AD. We found that additionally the structure of multi-spine boutons (MSBs) changes so that MSBs contain a higher number of spines than normal. These observations suggest that synaptic degeneration affects initially part of the synapse, either the pre- or post-synapse, and that the surviving part of the synapse abnormally connects to a neighbouring synapse. This leads to miswiring which should impair cognition. Moreover, our work suggests that a marker for presynaptic degeneration is an accumulation of the synaptic vesicle protein and co-chaperone CSPalpha in relative proximity of amyloid plaques. Finally, amyloid induces increased protein synthesis regulated by CYFIP2, causing an amplification of amyloid production, tau hyperphosphorylation, gliosis and memory loss.

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VISUALIZING REACTIVE ASTROCYTE-NEURON INTERACTION IN ALZHEIMER'S DISEASE USING 11C-ACETATE AND 18F-FDG PET/CT

Mijin Yun

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Theme 1 - Aging and Neurodegenerative diseases

Clinically validated neuroimaging probe to visualize the reactive astrogliosis are yet to be discovered. Here, we show that PET imaging with 11C-acetate and 18F fluorodeoxyglucose (18F-FDG) functionally visualizes the reactive astrocyte-mediated neuronal hypometabolism in the brains with neuroinflammation and AD. To investigate the alterations of acetate and glucose metabolism in the diseased brains and their impact on the AD pathology, we adopted multifaceted approaches including microPET imaging, autoradiography, immunohistochemistry, metabolomics, and electrophysiology. Two AD rodent models, APP/PS1 and 5xFAD transgenic mice, one adenovirus-induced rat model of reactive astrogliosis, and post-mortem human brain tissues were used in this study. We further curated a proof-of-concept human study that included 11C-acetate and 18F-FDG PET imaging analyses along with neuropsychological assessments from 11 AD patients and 10 healthy control subjects. We demonstrate that reactive astrocytes excessively absorb acetate through elevated monocarboxylate transporter1 (MCT1) in rodent models of both reactive astrogliosis and AD. The elevated acetate uptake is associated with reactive astrogliosis and boosts the aberrant astrocytic GABA synthesis when amyloid-β is present. The excessive astrocytic GABA subsequently suppresses neuronal activity, which could lead to glucose uptake through decreased glucose transporter-3 in the diseased brains. We further demonstrate that 11C-acetate uptake was significantly increased in the entorhinal cortex, hippocampus and temporo-parietal neocortex of the AD patients compared to the healthy controls, while 18F-FDG uptake was significantly reduced in the same regions. Additionally, we discover a strong correlation between the patients' cognitive function and the PET signals of both 11C-acetate and 18F-FDG. We demonstrate the potential value of PET imaging with 11C-acetate and 18F-FDG by visualizing reactive astrogliosis and the associated neuronal glucose hypometablosim for AD patients. Our findings further suggest that the acetateboosted reactive astrocyte-neuron interaction could contribute to the cognitive decline in AD.

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GLIAL CELL INVOLVEMENT IN THE NEURODEGENERATIVE PROCESS IN TAUOPATHIES

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The microtubule-associated protein tau aggregates in multiple neurodegenerative diseases, causing inflammation. We have shown that astrocytes become dysfunctional very early on in the progression of tau pathology in P301S tau mice. We have also demonstrated that tau pathology is associated with microglia activation at later stages of the pathology. Moreover, we have shown that microglia phagocytose live neurons containing tau aggregates cultured from P301S tau mice due to neuronal tau aggregate-induced exposure of the "eat me" signal phosphatidylserine. We also found that after phagocytosing tau aggregate-bearing neurons, microglia become hypophagocytic while releasing seed-competent insoluble tau aggregates. These microglia express a senescence-like phenotype, demonstrated by acidic ß-galactosidase activity, secretion of paracrine senescence-associated cytokines, cellular stress and maturation of matrix remodeling enzymes, results that are corroborated in P301S mouse brains and ex vivo brain slices. These data show that microglia that have been activated to ingest live tau aggregates-bearing neurons behave hormetically, becoming hypofunctional while acting as vectors of tau aggregate spreading. All together, these results show that glial cells are critically involved in the development of neurodegeneration due to tau pathology.

Theme 1 - Aging and Neurodegenerative diseases

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PATHOLOGICAL EFFECT OF AGGREGATION PROTEIN ON THE BLOOD-BRAIN BARRIER IN NEURODEGENERATIVE DISEASE

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The brain is the center of cognitive function and it is protected by the existence of special vasculature called the blood-brain barrier (BBB), which is the maintenance of brain homeostasis and prevention of the delivery of toxic molecules into the brain. The disruption of the integrity of BBB is known to be closely related to the progression of neurodegenerative diseases (ND), such as Parkinson's disease (PD) and Alzheimer's disease (AD). In addition, aggregation-prone proteins are known to cause damage to the integrity of the BBB which can accelerate the progression of the ND. Here, we recently confirmed the pathological roles of aggregation-prone proteins including alpha-Synuclein (α-syn) and amyloid beta (Aß) on the normal function and integrity of the BBB and the pathophysiological mechanisms behind these phenomena.

Theme 1 - Aging and Neurodegenerative diseases

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GLUTAMATERGIC DRIVERS OF TAU PATHOLOGY IN THE HUMAN THALAMUS

Tim Viney

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Theme 1 - Aging and Neurodegenerative diseases

Deficits in spatial navigation and orientation are associated with early cognitive decline prior to Alzheimer's disease. The apparent spread of pathological misfolded forms of the Tau protein (pTau) across different areas of the cerebral cortex correlates with cognitive decline, and this is thought to be initially driven by the spread of pTau from the entorhinal cortex to the hippocampus. The anterior thalamus 'updates' spatial memories in the cortex by 'relaying' sensorimotor messages concerning orientation and space. We observed in post-mortem human thalamus that the anterodorsal nucleus is selectively vulnerable to pTau at all stages of disease progression, even in cognitively unimpaired cases. Using double-labelling pre-embedding immunohistochemistry and electron microscopy, we discovered that large glutamatergic presynaptic terminals from the mammillary body accumulated pTau, but corticothalamic terminals did not, even at the stage before Alzheimer's disease. Furthermore, we detected pTau+ filaments at both presynaptic and postsynaptic sites, suggesting a previously unrecognized subcortical route for the transsynaptic spread of Tau in the human brain. The anterodorsal nucleus contains a high density of head direction (HD) cells, but the neurochemical identity and synaptic targets of individual thalamic HD cells are unknown. We use extracellular recordings and juxtacellular labelling in awake mice to define single HD cells in order to make predictions about the consequences of their dysfunction in humans. Spatial orientation deficits, relating to activity in the anterodorsal thalamic nucleus, could be a good predictor of future cognitive impairment leading to Alzheimer's disease.

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POSTER PRIZE TALK-UK; THE ROLE OF AD PROTECTIVE VARIANT PLCΓ2-P522R IN MODULATING MICROGLIA MEDIATED CLEARANCE AND SYNAPTIC PRUNING

Shiden Solomon

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The microglial mediated neuroinflammatory system has emerged as a major contributor to the molecular and phenotypic changes observed in the AD brain, including excessive synaptic loss (synaptic pruning) and decreased Aβ clearance (Heneka et al., 2015). GWAS studies have identified a number of novel rare coding variants for late-onset AD (LOAD) in microglial-associated genes (Sims et al., 2017). Notably, a single nucleotide polymorphism in the phospholipase C-gamma 2 gene (PLCγ2) (Pro522Arg) was found to be protective against LOAD (Magno et al., 2019). PLCγ2 hydrolyses the membrane phospholipid PIP2 (1-phosphatidyl-1D-myo-inositol 4,5-bisphosphate) to the secondary messengers IP3 (myo-inositol 1,4,5-trisphosphate) and DAG (diacyl-glycerol) activating a wide range of downstream signalling cascades (Bunney and Katan, 2011). However, how the P522R variant of PLCγ2 attenuates pathologic insult in AD remains unknown. In this study, we investigated the role of PLCγ2-P522R protective variant in modulating microglia mediated Aβ and synaptosome uptake, which may underpin its protective nature in vivo. We also investigated the potential impact of PLCγ2-P522R on mitochondrial function and ATP production, which may contribute to maintenance of microglial metabolic fitness. In addition, we also focused on microglial activation status, lysosomal activity, and motility. Crucially, we also demonstrate that the protective capacity of the PLCγ2-P522R variant is critically linked to its dose (the number of modified alleles), highlighting the need for a better understanding of the specific impact this variant has on microglial function, and how these pathways may be manipulated to improve outcomes in AD.

POSTER PRIZE TALK-KOREA; ASTROCYTIC UREA CYCLE DETOXIFIES AMYLOID BETA-DERIVED AMMONIA WHILE IMPAIRING MEMORY IN ALZHEIMER'S DISEASE.

Yeon Ha Ju

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Alzheimer's disease (AD) is one of the foremost neurodegenerative diseases, characterized by beta-amyloid (Aβ) plaques and significant progressive memory loss. In AD, astrocytes are proposed to take up and clear Aβ plaques. However, how Aβ induces pathogenesis and memory impairment in AD remains elusive. We report that normal astrocytes show non-cyclic urea metabolism, whereas Aβ-treated astrocytes show switched-on urea cycle with upregulated enzymes and accumulated entering-metabolite aspartate, starting-substrate ammonia, end-product urea, and side-product putrescine. Gene silencing of astrocytic ornithine decarboxylase-1 (ODC1), facilitating ornithine-to-putrescine conversion, boosts urea cycle and eliminates aberrant putrescine and its toxic byproducts ammonia and H2O2 and its end product GABA to recover from reactive astrogliosis and memory impairment in AD. Our findings implicate that astrocytic urea cycle exerts opposing roles of beneficial Aβ detoxification and detrimental memory impairment in AD. We propose ODC1 inhibition as a promising therapeutic strategy for AD to facilitate removal of toxic molecules and prevent memory loss.

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ASTROCYTIC METABOLIC PLASTICITY

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Theme 2 - Plasticity

The lateral hypothalamic area (LHA) regulates food intake and energy balance. Although LHA neurons innervate adipose tissues, the identity of neurons that regulate fat is undefined. Here we identify show that GABRA5-positive neurons in LHA (GABRA5LHA) polysynaptically project to brown and white adipose tissues in the periphery. GABRA5LHA are a distinct subpopulation of GABAergic neurons and show decreased pacemaker firing in diet-induced obesity (DIO) mouse models in males. Chemogenetic inhibition of GABRA5LHA suppresses fat thermogenesis and increases weight gain, whereas gene-silencing of GABRA5 in LHA decreases weight gain. In DIO mouse model, GABRA5LHA are tonically inhibited by nearby reactive astrocytes releasing GABA, which is synthesized by MAOB Maob. Gene-silencing of astrocytic MAOB Maob in LHA facilitates fat thermogenesis and reduces weight gain significantly without affecting food intake, which is recapitulated by administration of a MAOB Maob inhibitor, KDS2010. We propose that firing of GABRA5LHA suppresses fat accumulation and selective inhibition of astrocytic GABA is a molecular target for treating obesity.

MYELIN PLASTICITY IN THE ADULT BRAIN: HOW, WHEN, AND WHY?

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Theme 2 - Plasticity

Myelination of axons plays a critical role in the functioning of the vertebrate nervous system by increasing the transmission speed and energy efficiency of neural processing (Nave, 2010; Salzer and Zalc, 2016). Recent studies have demonstrated that myelin is more dynamic than initially thought. Myelination can be stimulated by artificially exciting neuronal activity (Cullen et al., 2021; Gibson et al., 2014; Mitew et al., 2018), indicating that myelin plasticity, in addition to synaptic modification, might be one way in which experience can shape brain structure and function (Bonetto et al., 2021; Kaller et al., 2017; Xin and Chan, 2020). Indeed, changes in myelination and white matter (WM) microstructure have been consistently associated with learning in humans (Lakhani et al., 2016; Scholz et al., 2009) and rodents (Bacmeister et al., 2022; Sampaio-Baptista et al., 2013). In addition, adaptive myelination is proposed to regulate homeostatic coordination and oscillatory self-organization in local and large-scale brain networks (Dubey et al., 2022; Noori et al., 2020; Pajevic et al., 2022, 2014; Talidou et al., 2022). Thus, deficient myelin plasticity might lead to alterations in myelination and neural network activity that impair neurological function (Geraghty et al., 2019; Knowles et al., 2022). This talk will summarise our current understanding of when, how, and to what extend adaptive myelination might contribute to healthy brain function and highlight aspects of this dynamic cellular process that require further investigation.

UNDERSTANDING CELLULAR AND CIRCUIT BASIS OF MONOGENIC FORMS OF NEURODEGENERATIVE DISORDERS

Peter Kind

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Theme 2 - Plasticity

Abstract - TBC

NEUROBIOLOGY OF LEARNING TO LEARN

Ain Chung

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Learning and memory are fundamental cognitive processes that allow animals to persistently and stably store information and flexibly adapt to dynamic environments. My research has focused on how persistent changes to circuit functions allow our brain to acquire long-lasting memory while accomplishing sustained cognitive enhancement in new learning. First, I studied how cognitive control training induces general cognitive enhancement by altering hippocampal neural circuit function beyond forming specific and explicit memories. I showed that cognitive control facilitated learning new tasks and rapidly changed medial entorhinal cortex (MEC)-to-dentate gyrus (DG) synaptic circuit function, resulting in an excitatory-inhibitory sub-circuit change that persists for months. Specifically, cognitive control training increases inhibition that attenuates the DG response to MEC input and, through disinhibition, potentiates the response to strong inputs, pointing to overall signal-to-noise enhancement.

Theme 2 - Plasticity

PSYCHIATRIC RISK FROM A CALCIUM CHANNEL GENE: WHEN SYNAPTIC PLASTICITY GOES WRONG

Cezar Tigaret

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Theme 2 - Plasticity

The CACNA1C gene encoding the pore-forming α1 subunit of CaV1.2 L-type voltage-gated Ca2+ channels (L-VGCCs) has been identified as cross-disorder risk gene for psychiatric conditions including schizophrenia and bipolar disorder. Common CACNA1C risk variants are intronic and are likely to alter CACNA1C gene expression, with recent studies indicating a reduced CACNA1C expression in the hippocampus. To translate genetics to neurobiological mechanisms we investigated the impact of reduced CACNA1C dosage on rat cognitive, synaptic and circuit phenotypes implicated by patient studies.

We show that rats hemizygous for Cacna1c (Cacna1c+/- rats) have disrupted Hebbian synaptic plasticity and circuit activity in the hippocampus culminating in marked impairments in learning to disregards non-salient stimuli, a behavioural deficit preciously associated with schizophrenia.

The activation of ERK pathway by a small-molecule BDNF mimetic compound acting at TrkB/C receptors rescued both the synaptic plasticity and behavioural deficits in Cacna1c+/- rats, indicating that the functional consequences of genetic variation in CACNA1C can be compensated by targeting the signalling mechanisms activated by L-VGCCs.

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PLENARY TALK; NMDA RECEPTORS AND LTP IN THE HIPPOCAMPUS

Graham Collingridge

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Professor Graham Collingridge, FRS, CBE, is the Director of the Tanz Centre for Research in Neurodegenerative Diseases (CRND), a Professor in the Department of Physiology at the University of Toronto, and a Senior Investigator at the Lunenfeld-Tanenbaum Research Institute at Mount Sinai Hospital, Toronto. Educated in the UK, he received a BSc in Pharmacology from the University of Bristol and a PhD from the School of Pharmacy, University College London in the field of neuroscience. Following postdoctoral appointments at the University of British Columbia (UBC), in Vancouver, and at the University of New South Wales, in Sydney, he returned to the UK to establish a laboratory at the University of Bristol. He has served as Chairs of the Department of Pharmacology at the University of Birmingham (UK), the Department of Anatomy at the University of Bristol and, most recently, the Department of Physiology at the University of Toronto. He was the founding Director of the MRC Centre for Synaptic Plasticity at the University of Bristol from 1999 until 2012 and retains a post within the School of Physiology, Pharmacology and Neuroscience in Bristol. Collingridge has held visiting ships at UBC and at Seoul National University, in South Korea. He has served as the President of the British Neuroscience Association and is currently the President of the Canadian Physiological Society. He served as Editor-in-Chief of Neuropharmacology from 1993 until 2010 and is currently a reviews editor for Molecular Brain. He is a Founder Fellow of the European DANA Alliance and a Founder Fellow of the Academy of Medical Sciences (UK). In 2001 he was elected a Fellow of The Royal Society.

TITLE-TBC

Athena Akrami

University College London

Email:

Theme 3 - Circuitry/ Computation

Abstract - TBC

BRAIN THETA STATE: BIOMARKER FOR COGNITIVE PERFORMANCE

Alan Jung Park

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Theme 3 - Circuitry/ Computation

Flexibly adapting to novel challenging situations is critical for survival, as we are experiencing during the pandemic. Notably, this flexibility is impaired in many neuropsychiatric disorders including autism and schizophrenia. Thus, understanding whether and how novel experience impacts brain circuitry to facilitate cognitive flexibility has important translational relevance. Here we show that novel experience resets theta (4-12 Hz) oscillatory state of the ventral hippocampus (vHPC) and the medial prefrontal cortex (mPFC), facilitating the ability to overcome an established strategy. Exposing mice to novelty disrupted a previously encoded strategy by reorganizing vHPC activity to local theta oscillations and weakening existing vHPC-mPFC connectivity. As mice subsequently adapted to a new task, vHPC neurons developed new task-associated activity, vHPC-mPFC connectivity was strengthened, and mPFC neurons updated encoding with new rules. Without novelty, however, mice adhered to their established strategy. Blocking dopamine D1-receptors (D1Rs) or inhibiting novelty-tagged cells expressing D1Rs in the vHPC prevented these behavioral and physiological effects of novelty. Furthermore, activation of D1Rs mimicked the effects of novelty. These results suggest that novelty promotes adaptive learning by D1R-mediated resetting of vHPC-mPFC circuitry, thereby enabling subsequent learning-associated circuit plasticity. Because many neuropsychiatric disorders are associated with altered theta state, our study provides new mechanistic insights for potential therapeutic interventions.

INPUT-DEPENDENT MICROMODULES IN THE CEREBELLAR INPUT LAYER : ANATOMICAL DETECTION AND COMPUTATIONAL MODELING OF THE EMERGENT PROCESS

Taegon Kim

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Theme 3 - Circuitry/ Computation

The cerebellar granule cell layer (GCL) refines inputs through mossy fiber (MF)-granule cell (GC) connections and relays them to Purkinje cells (PCs) via GC axons, parallel fibers (PFs). Considering the short dendrites of GCs, the connection probability of the MF-GC network was often assumed to be distance-dependent between them. By labeling two separate subgroups of GCs through our developmental phase-dependent labeling technique and ratiometric analysis compared with the network models, we showed that the MF-GC network has subtle heterogeneity that correlates with the developmental order of GCs. We also showed that GC developmental order-dependent heterogeneity in MF-GC connection correlated with MF origins such as dorsal column nuclei (DoCN) or pontine nuclei (PN). Because the subtle input-dependent heterogeneity could be interpreted as highly overlapping modules conveying different information, we developed a computational model that emulates the MF-GC network construction process. The model included the gradual migration and positioning of GCs and an origin-dependent MF maturation time and allowed MFs and GCs to connect based on Euclidean distance and the coincidence of postulated spontaneous activities. Our model could regenerate the heterogeneity and parametrize its extent. Additionally, the scenario based on synaptic weight-dependent pruning or module overlapping confirmed the regeneration of our prior model results. These imply that GCL may blend multimodal input information and provide a fused representation onto PCs. Further analysis of the resultant network parameters may reveal how GCL precisely orchestrates a variety of inputs for tasks where accuracy matters, such as smooth motor control.

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CORTICAL LAYER WITH NO KNOWN FUNCTION

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Theme 3 - Circuitry/ Computation

The lowermost cell layer of the cerebral cortex that contains interstitial white matter cells in humans has great clinical relevance. These neurons express higher proportions of susceptibility genes linked to human cognitive disorders than any other cortical layer and their distribution is known to be altered in schizophrenia and autism (Hoerder-Suabedissen et al., 2013; Bakken et al., 2016). In spite of these clinical links, our current knowledge on the adult layer 6b is limited. These cells are the remnants of the subplate cells that are present in large numbers and play key role in the formation of cortical circuits but a large fraction of them die during postnatal development. The adult population that remains in all mammals to form interstitial white matter cells in human or layer 6b in mouse display unique conserved gene expression and connectivity (Hoerder-Suabedissen et al., 2018). We study their input and output using combined anatomical, genetic and physiological approaches. Selected cortical areas, relevant for sensory perception, arousal and sleep (V1, S1, M1, prefrontal cortex) are studied using chemogenetic and optogenetic methods. Our preliminary data suggest that 6b is not just a developmental remnant cell population in the adult, but a layer that plays a key role in cortical state control, integrating and modulating information processing (Guidi et al., 2016; Molnar et al., 2020).

NEURAL REPRESENTATION OF COGNITIVE-MOTOR INTEGRATION IN BASAL GANGLIA OUTPUTS

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Integration of cognitive-motor function is essential for survival. To do this, each motor program must be properly linked to the cognitive process and turned on or off depending on the situation. When they collapse, it causes many severe neurological disorders. Although basal ganglia output regions including the thalamus have massive convergence inputs from the cortex and subcortical areas, the underlying mechanism for cognitive-motor integration is largely unclear. Our goal is to unravel the neural circuits and specific cell types that are important to integrate and properly turn a series of actions on and off. Combining optogenetics, deep brain calcium imaging, and mathematical classifications, we found that the thalamus has distinct ensemble clusters for behavioral sequences. Also, we are going to introduce novel cell types that are critical for the integration of cognitive function. These suggest that this novel circuitry might be a new therapeutic target for neurological disorders that show impaired cognitive-motor integrations, such as ASD or OCD.

Theme 3 - Circuitry/ Computation

The 14th UK-KOREA
NEUROSCIENCE SYMPOSIUM
15 - 16th August, 2023 (9 am - 5 pm)

ROLES OF SLEEP OSCILLATIONS IN MOTOR MEMORY CONSOLIDATION

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Theme 3 - Circuitry/ Computation

Sleep contributes to the consolidation of both declarative and motor memories. Declarative memory is our ability to acquire and recall facts and events, while motor memory is our capacity to acquire various skills like shoe lacing or playing an instrument. A large body of studies has proposed the roles of sleep oscillations for declarative memories. Yet, direct evidence for the neural basis is lacking for motor memory systems. My studies focus on motor learning and memory and understanding sleep-dependent mechanisms using in vivo electrophysiology and techniques like brain-machine interfaces and reach-to-grasp tasks in rodents. My presentation will cover two parts of recent findings: 1 sleep slow-oscillations (SO) and delta-waves (δ) play dissociable roles in memory consolidation versus forgetting (Kim et al., Cell, 2019), 2 two-stage role of hippocampal sharp-wave ripples and cross-area coordination in motor memory consolidation and cortical manifold learning (Kim et al., Nature, 2023).

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HUMAN STEM CELLS MODELS OF FAMILIAL ALZHEIMER'S DISEASE AND FAMILIAL BRITISH DEMENTIA

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Theme 4 - Novel Methods

Alzheimer's disease (AD) and other forms of dementia represent a significant public health challenge due to the absence of disease-modifying therapies. A significant challenge in the development of novel therapies is the lack of appropriate pre-clinical models and poor translation of candidate therapeutics from The development of human induced pluripotent stem cells (iPSC) and their subsequent differentiation into neurons, astrocytes, microglia and 3D organoid cultures has provided new opportunities for the generation of physiologically relevant, in vitro disease models. I will present our work using these to generate novel, early stage models of dementia.

We have generated a cohort of iPSC from individuals with rare, genetic forms of dementia including familial Alzheimer's Disease (FAD), familial British Dementia (FBD). I will discuss the mutation-specific effects of FAD associated APP and PSEN1 mutations on APP processing and A? generation in neurons, and how these have revealed distinct underlying mechanisms that may contribute to clinical heterogeneity in disease. Recently, the critical contribution of non-neuronal cell types to disease pathogenesis has become apparent. I will discuss our data showing an important and previously unknown role for microglia in rare dementias linked to the ITM2B/BRI2 gene, which include familial British dementia and familial Korean dementia. Together, our models give us unique insight into the diversity of amyloids involved in dementia and the contributions of different cell types to amyloid generation, which will inform the development of novel therapies for AD and other dementias..

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SCULPTING NEURAL CIRCUITS VIA DESIGNED NEURO-GLIA INTERACTION

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Theme 4 - Novel Methods

The brain is composed of an incredibly complex network of interconnections among various cell types, through which they communicate to control diverse brain functions including cognition, emotion, movement, and memory. Although remarkable technical advances have been made in controlling the electrical activity of neurons, methods for modulating the physical connections between neurons are still lacking. In this talk, I will present a synthetic molecular approach for selectively modulating the structure of target neural circuits through engineered neuro-glia interactions. We have designed synthetic ligand and receptor proteins to induce direct cell-cell conjugates, leading to unidirectional transfer of ligands to receptor-expressing cells, similar to a process known as 'trogocytosis'. In cultured neurons and astrocytes, we observed active engulfment of membrane fragments of neurons by astrocytes following the application of synthetic trogocytosis. Additionally, in the hippocampus, induction of synthetic trogocytosis of CA3 neurons by CA1 astrocytes resulted in structural and functional modulation of the CA3-CA1 circuit, validated by immunohistochemistry, electron microscope imaging, electrophysiology, and behavioral analyses. Through further engineering and characterization, synthetic trogocytosis will offer a powerful means for manipulating neural connections in both space and time, and contribute to a better understanding of the physiological implications of complex, yet finely tuned, neural networks.

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EXPLORING DIFFERENT PLAQUE ENVIRONMENTS IN ALZHEIMER'S DISEASE USING SPATIAL TRANSCRIPTOMICS

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The amyloid plaque cell niche is a pivotal hallmark of Alzheimer's disease (AD). Where early spatial transcriptomics (ST) technologies have provided valuable information on transcriptomic alterations in the small tissue domains overlaying with amyloid plaques, they lacked cellular resolution. I will talk about two novel high-resolution ST platforms, CosMx and Stereo-seq, and their ability to characterize the cellular response in the amyloid plaque niche in an AD mouse model. We found highly microglial-astrocytic responses across the amyloid plaque micro-environment and studied how these responses could relate to neuronal transcriptomic alterations.

Theme 4 - Novel Methods

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NEURAL INTERFACE TECHNOLOGIES FOR HIGH RESOLUTION INTRAOPERATIVE BRAIN MAPPING

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Theme 4 - Novel Methods

Electrophysiological devices are critical for mapping eloquent and diseased brain regions and therapeutic neuromodulation in clinical settings and are extensively utilized for research in brain-machine interfaces. However, the existing devices are often limited in either spatial resolution or cortical coverage. Here, we developed scalable manufacturing processes and dense connectorization to achieve reconfigurable thin-film, multi-thousand channel neurophysiological recording grids using low impedance platinum-nanorods (PtNRGrids).

In the clinical setting, PtNRGrids resolved fine, complex temporal dynamics from the cortical surface in an awake human patient performing grasping tasks. High gamma activities (HGAs) showed distinctive neural correlates of hand movements when compared to baseline. We also recorded phase reversal boundaries during motor mapping to precisely localize the central sulcus in mm scale resolution. Additionally, the PtNRGrids identified the spatial spread and dynamics of epileptic discharges in a patient undergoing epilepsy surgery, including activity induced by direct electrical stimulation.

Furthermore, to provide automated and real-time feedback directly from the cortical surface for efficacious and high-precision neurosurgery, we integrated a flexible micro-LED display with PtNRGrids. This system recorded the cortical activities, processed the data in real time, and displayed brain mapping information on the cortical surface. On top of the pig's brain, the LED+ECoG grid displayed the cortical functional boundary, HGAs, and the propagation of interictal discharges. By visualizing the cortical functional boundaries to the neurosurgeon, this technology has the potential to significantly shorten surgical time and enhance the precision of resective neurosurgery.

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MULTIMODE OPTICAL FIBRES AS FLEXIBLE HAIR-THIN ENDOSCOPES FOR HIGH RESOLUTION DEEP NEUROIMAGING

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Multimode optical fibres (MMFs) are hair-thin endoscopic probes that have allowed minimally invasive in vivo neuroimaging in deep-brain regions. MMFs efficiently deliver light to and from an imaging site with a footprint of less than 200 µm while simultaneously achieving diffraction-limited spatial resolution. However, there is a major limitation in MMF imaging - overcoming distortions to the light propagation induced by physical deformations of the fibre. Fibre bending destroys the focus quality of light travelling through an MMF and hence significantly worsens image quality. This presentation will outline endoscopic MMF neuroimaging and our approach to correcting bending-induced distortions, ultimately working towards fully flexible endoscopic MMF imaging probes.

Theme 4 - Novel Methods

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TRACKING MICROGLIA AND IMMUNE CELLS WITH A FLUORESCENT SMALL MOLECULE

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Fluorescent small molecules have long been used as a probe for biomolecules such as nucleotides and proteins. Here, we show a novel molecule having fluorescence substrate activity to a single enzyme in live animal cells, developed by a forward chemical screening using brain cells. The successful candidate chemical was specialized to label microglia, and the mechanism study revealed that it uses the Ugt1a7c-mediated fluorescence turn-on process. Because of its unique fluorescence-labeled mechanism and high penetration activity in live tissue, the probe tracks microglia at tissue levels by simple bathing or intravenous injection. Further modifications of this promising compound without disturbing its specificity to the Ugt1a7c enzyme led to the development of a new toolset for labeling microglial subcellular structures or biomolecules. Moreover, because of the specificity of Ugt1a7c in immune cell types, the probe could track monocytes and neutrophils in peripheral blood as well as microglia in CNS, expanding its application to the biomedical field.

Theme 4 - Novel Methods

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Poster Session (Grove Auditorium)

Grove Auditorium,

The Greek proportions have been maintained within the building, with an entrance Foyer or Gallery the full height of the building offering a space for registration, refreshments and receptions. Exhibitions can be held or material displayed on large panels suspended below a collection of tapestries designed by John Piper.

Adjoining the Foyer are a small cloakroom area and toilets. The Auditorium and Foyer are fully accessible by wheelchair, and WiFi Internet is available.

Magdalen College
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POSTER 1 - SHANK3-L68P MUTANT MICE SHOW REDUCED SOCIAL COMMUNICATION AND COGNITIVE INFLEXIBILITY AND IMPAIRED MGLUR-LTD

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POSTER

Shank3 is an excitatory postsynaptic scaffolding protein implicated in multiple brain disorders, including autism spectrum disorders (ASD), Phelan-McDermid syndrome, schizophrenia, intellectual disability, and mania. Previous in vitro studies on the patient-derived Shank3-L68P mutation, affecting the N-terminal SPN domain of the protein, revealed that it induces changes in the protein structure and interactions, although its pathophysiology in vivo remains unclear. Here we generated and characterized a Shank3 knock-in mouse line carrying the L68P mutation (Shank3-L68P mice). These mice show impaired social communication, enhanced self-grooming, reduced digging, and cognitive inflexibility. Hippocampal Shank3-L68P transcripts show patterns similar to those observed in ASD and downregulated synaptic genes. Hippocampal Shank3-L68P neurons show decreased excitatory synaptic transmission and impaired mGluR-LTD without changes in NMDA-dependent LTP or LTD. Impaired mGluR-LTD in Shank3-L68P was rescued by CDPPB. RNA-Seq and proteomics analyses point to alterations in local protein translation and actin regulation. These results suggest that the Shank3-L68P mutation leads to behavioural deficits in mice accompanying altered mGluR-LTD and synaptic signaling.

POSTER 2 - UNDERSTANDING THE FUNCTION OF NEURODEVELOPMENTAL DISORDER-ASSOCIATED PHF14 COMPLEX IN DNA DAMAGE RESPONSE

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POSTER

Among the genes associated with neurodevelopmental disorders (NDD), a substantial portion are involved in chromatin regulation. We found that a putative chromatin-associated protein complex consisting of PHF14, HMG20A, TCF20 and RAI1 participate in DNA damage response and forms LLPS droplets which contain DNA through HMG20A, a DNA binding protein. Phf14 knockout neural progenitor cells exhibit decreased DNA repair and impaired cell cycle progression and proliferation. Both TCF20 and RAI1 interact with PHF14 and HMG20A and all four proteins rapidly localize to DNA damage sites and maintained there. Importantly, TCF20 facilitates droplet formation and its maintenance at DNA damage sites is destabilized upon a pathological mutation found in NDD patient with intellectual disability and autistic features. This mutation leads to the loss of the PHF14 and HMG20A interacting regions. Together, we suggest that the disruption of the PHF14 complex function by TCF20 pathological mutation as a mechanism that might lead to the development of NDD.

POSTER 3 - DELETION OF PHOSPHOLIPASE C ETA 1 IN HABENULA ASTROCYTES INDUCES DEPRESSIVE BEHAVIOR IN MICE

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POSTER

Phospholipase C (PLC) enzymes play a crucial role in intracellular calcium-signaling transduction, mediating cellular activities in the brain. In astrocytes, PLC involves in the release of gliotransmitters such as glutamate by increasing intracellular calcium, which contributes to neural activity. Recently PLCη subtype has been identified and is known to be enriched in astrocytes. However, its physiological function is not yet fully understood. This study aimed to investigate the role of the PLCη1 subtype in the lateral habenula (LHb) astrocytes and its potential impact on mood behavior. Here, we show that genetic deletion of PLCη1 in astrocyte reduces morphological complexity, as indicated by decreased total process length and the number of branches in Aldh1l1-CreERT2; Plch1f/f mice. We also found a reduced tonic AMPAR/NMDAR current, increased synaptic efficacy, and impairment of extrasynaptic long-term depression (LTD) in the LHb. Furthermore, silencing of astrocytic PLCη1 in LHb by injection of AAV-Gfap-Cre into LHb of Plch1f/f mice, showed depressive-like behaviors, including helplessness and anhedonia, without affecting anxiety, locomotion, or cognitive functions. Lastly, we found a decreased expression of Plch1 mRNA in mice after restraint stress, a well-known depression-like behavior model. Our findings reveal a previously unexplored role of PLCη1 in LHb astrocytes for shaping morphologies and neuronal activities associated with mood regulation.

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POSTER 4 - A MULTI-OMIC INVESTIGATION OF IPSC-DERIVED NEURONS FROM SPORADIC PD

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POSTER

Up to 85% of people with Parkinson's disease have no family history and no defined monogenic cause of the disease with age the biggest risk factor for Parkinson's. Given the lack of defined genetic cause, it was hypothesised that loss of epigenetic marks during iPSC-reprogramming would result in common Parkinson's phenotypes being absent in iPSC-derived dopaminergic neurons derived from sporadic Parkinson's patients.

To test this, we differentiated iPSC lines from sporadic patients into dopaminergic neurons. Neurons were profiled by proteomics, transcriptomics, metabolomics and lipidomics. We identified that the proteomic signature of sporadic patient neurons clustered away from control neurons with a number of pathways including autophagy, oxidative stress and cholesterol biosynthesis identified as perturbed in sporadic patients. However, importantly, this clustering was not observed with the transcriptomic signature.

We confirmed these pathways and demonstrated impaired mitochondrial function, alongside changes in autophagy and ER stress in a subset of sporadic patients. In addition, changes in amino acid biosynthesis and lipid levels were observed by metabolomics and lipidomics, respectively.

This study demonstrates the utility of iPSC-derived neurons for investigating sporadic disease and demonstrates overlap with cellular phenotypes observed in iPSC-derived neurons derived from monogenic Parkinson's patients.

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POSTER 5 - ANTIPARKINSONIAN MEDICATION MASKS MOTOR SIGNAL PROGRESSION IN DE NOVO PATIENTS

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POSTER

Patients not yet receiving medication provide insight to drug-naïve early physiology of Parkinson's Disease (PD). Wearable sensors can measure changes in motor features before and after introduction of antiparkinsonian medication. We aimed to identify features of upper limb bradykinesia, postural stability, and gait that measurably progress in de novo PD patients prior to the start of medication, and determine whether these features remain sensitive to progression in the period after commencement of antiparkinsonian medication.

Upper limb motion was measured using an inertial sensor worn on a finger, while postural stability and gait were recorded using an array of six wearable sensors. Patients were tested over nine visits at three monthly intervals. The timepoint of start of medication was noted.

Three upper limb bradykinetic features (finger tapping speed, pronation supination speed, and pronation supination amplitude) and three gait features (gait speed, arm range of motion, duration of stance phase) were found to progress in unmedicated early-stage PD patients. In all features, progression was masked after the start of medication.

Commencing antiparkinsonian medication is known to lead to masking of progression signals in clinical measures in de novo PD patients. In this study, we show that this effect is also observed with digital measures of bradykinetic and gait motor features.

POSTER 6 - DYSREGULATED BASAL MITOPHAGY, NEURONAL ACTIVITY AND SYNAPTIC PLASTICITY IN IPSC-DERIVED DOPAMINERGIC NEURONS WITH AN ALPHA-SYNUCLEIN GENE TRIPLICATION MUTATION

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POSTER

α-Synuclein accumulation in Lewy bodies in the brain is one of the hallmarks of Parkinson's disease (PD), which predominantly affects dopaminergic neurons in the substantia nigra pars compacta. α Synuclein has been linked to dysfunctional degradation of mitochondria or mitophagy and impaired neuronal activity and synaptic plasticity, however the exact mechanisms how α-synuclein contributes towards these phenotypes are poorly understood, in part because of a lack of informative human model systems. Here, we have characterised induced pluripotent stem cell (iPSC)-derived dopaminergic neurons from a patient with an α synuclein (SNCA) gene triplication mutation, which causes a rare form of early-onset familial PD, and compared these to neurons from healthy volunteers. Using the live cell mitophagy mt-Keima fluorescent reporter, we found that under basal conditions SNCA triplication neurons showed an increase of mitochondria located in lysosomes compared to control neurons 35-50 days post-differentiation. No significant changes were seen in mitophagy induced by mitochondrial membrane depolarisation, suggesting that this process is PINK1-Parkin independent. A neuronal activity assay using multi-electrode arrays (MEAs) revealed that SNCA triplication neurons had significantly reduced firing rates and bursting events and presented 60 days post-differentiation. Moreover, SNCA triplication neurons displayed impaired long-term potentiation (LTP) upon stimulation using a chemically-induced LTP protocol. These combined results suggest that mitochondrial dysfunction driven by α synuclein, may precede impairment of neuronal activity. Further investigations are underway to pinpoint how α synuclein dysregulates basal mitophagy and to elucidate the connection with the observed reduction in neuronal activity and cLTP.

POSTER 7 - IN VITRO MODELLING OF THE MECHANISMS OF IMMUNE EFFECTOR CELL ASSOCIATED NEUROTOXICITY SYNDROME (ICANS) RESULTING FROM CAR T CELL THERAPY TREATING HAEMATOLOGICAL MALIGNANCIES

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POSTER

Introduction of chimeric antigen receptor (CAR) T-cell therapy has greatly improved the prognosis of haematological malignancies. However, its usage is limited due to adverse toxicities such as immune effector cell-associated neurotoxicity syndrome (ICANS). ICANS presents with neurological and cognitive deficits, which can progress to seizures, coma, and death. The underlying pathophysiology of ICANS is not well understood, but it is associated with excessive cytokine release and blood-brain barrier dysfunction. My PhD project aims to investigate the mechanisms linking CAR-T cells to ICANS by co-culturing activated anti-CD19 and anti-BCMA CAR-T cells and their secreted factors with central nervous system (CNS) cells in vitro. Human umbilical vein endothelial cells (HUVECs) will be initially used to optimize co-culture assays. Induced pluripotent stem cell (iPSC) technology will then be employed to derive CNS cells, including neurons and microglia, to model the neurovascular unit. Phenotypic and functional changes in CAR-T and CNS cells will be characterized, and their recapitulation in ex vivo cultures of resected brain tissue will be assessed. Identifying the pathways involved in ICANS pathology could potentially lead to preventive or alleviative strategies for this condition.

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POSTER 8 - GLUTAMATERGIC DRIVERS OF TAU PATHOLOGY IN THE HUMAN THALAMUS

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POSTER

Aggregation and propagation of misfolded pathological Tau proteins (pTau) correlate with the severity of neurological symptoms of tauopathic neurodegenerative diseases. Alzheimer's disease, a secondary tauopathy, involves the apparent spread of pTau from the entorhinal cortex to other cortical areas including hippocampus. Early symptoms include impairments in memory recall and a decline in spatial navigational abilities. Tracking and explaining the spread of pTau may shed light on the mechanisms that link Tau pathology with neurodegeneration. Since animal models might not recapitulate the neuroanatomical and neurochemical characteristics of propagation, we immunohistochemically investigated the distribution of pTau in human post-mortem cortical and thalamic brain sections from cases with no apparent cortical Tau pathology (early stages), moderate pathology (middle stages), and Alzheimer's disease (late stages). The anterior group of thalamic nuclei are required for spatial memory; we found that the anterodorsal thalamic nucleus (ADn) accumulated pTau at the earliest stages of disease progression. Moreover, we observed that a calretinin-expressing subpopulation of ADn neurons were especially vulnerable to pTau accumulation at all stages of disease progression. Electron microscopy revealed that pTau was present in both pre- and postsynaptic sites in the ADn, suggesting the transsynaptic spread of pTau. Finally, we found that pTau immunopositive boutons preferentially co-localised with vesicular glutamate transporter-2, which is present in mammillothalamic inputs, while corticothalamic terminals were largely unaffected. We suggest a parallel or alternative subcortical route for the propagation of pTau from the mammillary nucleus via the thalamus in the human brain in relation to Alzheimer's disease.

POSTER 9 - NEUROMODULATION BY ULTRASOUND: THE EFFECTS OF 40HZ STIMULATION ON NEUROTROPHIC SIGNALLING IN THE HIPPOCAMPUS

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POSTER

Aberrant gamma oscillations underlie the pathogenesis of several neurodegenerative diseases. Focused ultrasound stimulation (FUS) is an effect neuromodulator and could potentially be used to entrain gamma oscillations. However, mechanistic understanding of ultrasound's neuromodulatory effects remains limited. Therefore, we explored the effects of FUS on a key mediator of synaptic plasticity and neural growth, brain-derived neurotrophic factor (BDNF). We exposed acute hippocampal slices to 40 Hz pulsed ultrasound and investigated the effects on BDNF production. Immunoblot analysis revealed a notable increase in BDNF expression in the hippocampal slices following 1 hr of 40 Hz exposure. This effect was not observed with shorter stimulation durations or lower and higher pulsed frequencies, underscoring the critical significance of utilising the 1 hr 40 Hz protocol. Our preliminary in vivo rat experiments also indicate an increase in BDNF expression following transcranial ultrasound exposure. Overall, our results indicate that ultrasound has modulatory effects on BDNF signalling. The data highlights the potential of this approach for therapeutic uses.

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POSTER 10 - THE TAU N-TERMINAL DOMAIN IMPACTS THE DEGREE OF PATHOPHYSIOLOGY INDUCED BY TAU PHOSPHORYLATION IN HIPPOCAMPAL CA1 NEURONS

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POSTER

The aberrant posttranslational modification of Tau, resulting in its hyperphosphorylation, is known to be a contributing factor to synapse weakening in multiple neurodegenerative disorders (e.g., Alzheimer's Disease). Interestingly, alternative splicing can result in six different Tau isoforms. However, a knowledge gap exists between tau isoform subtype and the pathophysiological role they play in synapse function. Specifically, the role of the tau 1N4R isoform, the most abundant isoform in the human brain, remains poorly understood. This study aimed to investigate the role of the tau n-terminal domain (e.g., 1N4R vs 2N4R) in mediating hyperphosphorylation induced pathophysiology.

Organotypic hippocampal slice cultures from rats were biolistically transfected with either tau 2N4R phosphomimic (Tau-PHF1E) or tau 1N4R phosphomimic (Tau-PHF1E ΔN2), along with a structural marker. We analysed the basal synaptic transmission, single spine structural plasticity and spine density in CA1 pyramidal neurons. The results revealed that Tau (2N4R)-PHF1E expression led to a reduction in synaptic current mediated by AMPA receptors and a decrease in synapse density within CA1 neurons. Moreover, Tau (2N4R)-PHF1E impaired spine plasticity in CA1 neurons by multiphoton-glutamate uncaging stimulation. Notably, Tau-PHF1E ΔN2 expression (e.g., 1N4R isoform of tau) did not produce the deficits observed in Tau-PHF1E. The findings suggest that there is a distinct process of pathophysiology between 1N4R and 2N4R tau in CA1 neurons. Collectively, these novel findings enhance our understanding of the consequences of tau phosphorylation status and tau-isoform subtype in driving the underlying mechanisms of aberrant synapse weakening within the hippocampus.

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POSTER 11 - AMYLOID BETA RECRUITS CA2+ RELEASE FROM THE ENDOPLASMIC RETICULUM FOLLOWING BACK-PROPAGATING ACTION POTENTIALS IN HIPPOCAMPAL CA1 NEURONS

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POSTER

The dysregulation of intracellular Ca2+ homeostasis in Alzheimer's Disease (AD) is associated with abnormal synaptic plasticity, an early hallmark of disease pathogenesis. A number of studies have demonstrated that amyloid beta (Aβ) increases the level of Ca2+ in neurons, causing intracellular Ca2+ overload and ultimately neuronal death. Given the relationship between dysfunctional intracellular Ca2+ signalling and AD, we examined whether activity-dependent aspects of Ca2+ signalling, such as Ca2+ release from the intracellular stores, are altered by Aβ.

CA1 hippocampal neurons were loaded with the Ca2+-sensitive dye, OGB-1, and confocal imaging was performed to measure the dendritic Ca2+ rise that accompanies a back-propagating action potential (bpAP). The addition of 200 nM Aβ for 1 hour significantly increased the peak Ca2+ signal (in arbitrary units, peak change in Ca2+ signal - Control: 1.91 ± 0.064; Aβ: 2.42 ± 0.071; n=6) following a bpAP. Pharmacological dissection of the signal revealed that the Aβ driven increase arises from the release of Ca2+ from the endoplasmic reticulum (ER) as the application of ryanodine or thapsigargin returns the Ca2+ signal to control levels (Control: 1.87 ± 0.082; Aβ: 2.40 ± 0.12; ryanodine + Aβ: 1.83 ± 0.061; thapsigargin + Aβ: 2.03 ± 0.060; n=6). This result is surprising as it suggests that Aβ recruits Ca2+-induced Ca2+ release from the ER in response to a bpAP, something that does not ordinarily occur in CA1 neurons.

POSTER 12 - A HIGH THROUGHPUT ASSAY TO INVESTIGATE CA1 LOCAL NETWORK ACTIVITY: MODELS FOR PHYSIOLOGY AND PATHOPHYSIOLOGY

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POSTER

The hippocampus plays important roles in learning and memory. Growing evidence illustrates that Cornu Ammonis 1 (CA1) plays a critical role in certain type of learning and memory. It was assumed that its excitatory neuronal coordination occurred only from upstream circuits. However, recent research identified that CA1 local circuits also actively transform the afferent information, which might structure cell assemblies that drive behaviour (Robinson et al., 2020). In that sense, understanding CA1 local network is becoming more important.

We are developing a new experimental approach using laser applied point stimulation and glutamate uncaging to visualise evoked neuronal network activity and monitor the response by intracellular Ca2+ imaging in organotypic hippocampus culture slices. We have validated that the activation of a CA1 neuron can cause the CA1-network activity which is indicative of CA1 local circuit connectivity. We also compared CA1 local circuit connectivity between physiological and pathophysiological models. In the control condition, glutamate uncaging induced a robust activation of the local CA1 network, illustrated by a spreading wave of calcium activity in neighbouring neurons. Subsequently, we utilised the synthesised oligomeric amyloid-beta model as previously documented (Jo et al., 2011; Whitcomb et al., 2015). Incubation with oligomeric amyloid-beta impaired the neuronal response, specifically lowering the number of activated neurons and altering the pattern of spread. Collectively, suggesting that this approach can be utilised to study the consequence of pathogen associated pathophysiology in CA1 local circuit connectivity.

POSTER 13 - FLEXIBLE NEURONAL MITOCHONDRIAL DYNAMICS CONTROL SLEEP

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POSTER

Sleep is ubiquitous and essential, but the molecular processes that call for and benefit from it remain elusive. The neural control of sleep requires that sleep need is sensed during waking and discharged during sleep. In Drosophila, sleep deprivation leads to the accumulation of reactive oxygen species (ROS) in the mitochondria of sleep-control neurons projecting to the dorsal fan-shaped body (dFBNs). This internal representation of sleep need is then translated into sleep by the redox-sensitive beta-subunit of the voltage-gated potassium channel Shaker, which regulates the excitability of the sleep-promoting cells via the oxidation state of a stably bound nicotinamide cofactor. To obtain a comprehensive, unbiased view of sleep need-dependent molecular changes in dFBNs, we characterized the transcriptomes of single cells isolated from the brains of rested and sleep-deprived flies. Genes upregulated after sleep deprivation, in dFBNs but not elsewhere in the brain, encoded virtually exclusively proteins with roles in mitochondrial respiration and ATP synthesis. These gene expression changes were accompanied by mitochondrial fragmentation, enhanced mitophagy, and an increase in the number of contacts between mitochondria and the endoplasmic reticulum.

The morphological changes were reversible after recovery sleep and blunted by the installation of an electron overflow pathway in the respiratory chain. Inducing mitochondrial fragmentation or fusion in dFBNs altered sleep and the electrical properties of sleep-control cells in opposite directions: hyperfused mitochondria increased, whereas fragmented mitochondria decreased, neural excitability and sleep duration. ATP levels in dFBNs rose after enforced waking, presumably because of diminished ATP consumption during the arousal-mediated inhibition of these neurons, which predisposes them to heightened oxidative stress. Consistent with this view, uncoupling electron flux from ATP synthesis relieved the pressure to sleep. The first single-cell transcriptome of an animal's sleep-control neurons at variable levels of sleep pressure thus suggests a causal and bidirectional link between cellular bioenergetics and sleep. Targeted mitochondrial manipulations validate the physiological importance of this link.

POSTER 14- DECODING HEREDITARY SPASTIC PARAPLEGIA PATHOGENIC MUTATION WITH BIOPHYSICS AND IN VIVO IMAGING

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POSTER

Hereditary spastic paraplegia (HSP) is a varied group of detrimental inherited neurodegenerative or neurodevelopmental disorders without any effective treatment available. Many gene mutations related to neuronal transport have been reported to be linked with HSP, indicating neuronal transport might be a good drug target for HSP. It has been documented that neuronal motor protein KIF1C is involved in the pathophysiology of HSP subtype SPAX2/SAX2, suggesting that specific therapy for unique gene mutations causing HSP is rational and promising. This project aims to decipher the roles played by KIF1C in HSP and explore the possibility of designing a therapeutic strategy for KIF1C-associated HSP treatment. We have found that two HSP pathogenic mutations P176L and R169W generates less force compared with healthy motto using optical trap.

The HSP in vivo model will be prepared by CRISPR/Cas9 technology at the one-cell stage to knockout KIF1C of zebrafish Danio rerio. Immunostaining and behavioural tests will be employed to detect defects in neuronal development and intracellular transport in KIF*1C knockout fish*. Identification of neuronal cargoes transported by KIF1C enables us to test which cargoes are mis-localised in HSP mutant fish. In addition, the human KIF1C mRNA will be used to reactivate intracellular transport in KIF1C knockout fish to investigate any improvement in term of neuronal development, intracellular transport and behaviours.

The 14th UK-KOREA
NEUROSCIENCE SYMPOSIUM
15 - 16th August, 2023 (9 am - 5 pm)

Dining in Hall

Formal and informal meals are taken in the mediaeval Hall, which is located on the first floor above the Cloisters. There is a lift (elevator) available for any with special access needs. The Hall has refectory style tables with chairs and some benches, seating up to 160 including 25 at the High Table.

For regular daily meals, guests help themselves from the assisted-service Buttery, and then carry their tray through to the Hall. This area of College is one of the most historic, and the nature of the space available to provide a free-flow assisted service facility is therefore limited. It is part of the tradition of taking meals in a College setting that guests spend some time queuing, but we are confident that the time spent chatting to colleagues will not be wasted!

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