Oral Abstracts

Alex Mellor

Acute Inflammation increases White Matter Sensitivity to Ischaemia

Ischaemic brain injuries are a major cause of disability worldwide, of which chronic inflammation is a risk factor. Up to 80% of ischaemic stroke and 90% of vascular dementia patients have white matter damage. Chronic infections increase circulating levels of pro-inflammatory mediators, including lipopolysaccharide; a component of Gram-negative cell walls which can cross the blood-brain barrier, having potent neuroinflammatory effects. The mechanisms behind the predisposition of those with chronic infections to ischaemic brain injuries are currently unknown. Here we show that white matter is sensitised to decreased functional recovery following ischaemia by lipopolysaccharides, caused by a sub-critical myelin injury. Compound action potential electrophysiology shows low, clinically relevant concentrations of lipopolysaccharides cause no functional changes within white matter, however when subject to combined low dose lipopolysaccharide and ischaemia, functional recovery of white matter decreases compared to ischaemia alone. This decreased recovery post-ischaemia is accompanied by a loss of myelin following combined lipopolysaccharide and ischaemia exposure, shown by vital myelin imaging using the fluorescent dye Fluoromyelin Red. Our results demonstrate that white matter, which exhibits a high degree of pathology in ischaemic brain injuries, is sensitised to ischaemic damage following chronic lipopolysaccharide, a pro-inflammatory mediator the CNS is exposed to during chronic infection. This suggests a mechanism behind the predisposition of those with chronic inflammation to increased risk of ischaemic brain injuries, including ischaemic stroke and vascular dementia. Further elucidating mechanisms behind this sensitisation paradigm may provide opportunity for prophylactically targeting white matter sensitisation to ischaemia in at-risk patients with chronic inflammation.

Luke Weymouth

An Epigenome-wide association study of psychosis in Alzheimer's disease

Psychosis is a debilitating syndrome occurring in 40-60% of people with Alzheimer’s disease (AD) and corresponds with a more severe disease course. Evidence suggests that psychosis in AD (AD+P) is associated with a distinct profile of neurobiological changes, but little is known about the molecular processes driving etiology. For this project we performed an epigenome-wide association study (EWAS) to investigate DNA methylation associated with AD+P.

Joshua Harvey

Linking Parkinson's disease and depression, epigenetic insights into midbrain neuronal changes

Parkinson’s disease is a highly heterogeneous disorder, encompassing a complex spectrum of clinical presentation including motor, sleep, cognitive and neuropsychiatric symptoms. We aimed to investigate genome-wide DNA methylation networks in post-mortem Parkinson’s disease brain samples and test for region-specific association with common neuropsychiatric and cognitive symptoms. Of traits tested, we identify a co-methylation module in the substantia nigra with significant correlation to depressive symptoms and with ontological enrichment for terms relevant to neuronal and synaptic processes. Notably, expression of the genes annotated to the methylation loci present within this module are found to be significantly enriched in neuronal subtypes within the substantia nigra. These findings highlight the potential involvement of neuronal-specific changes within the substantia nigra with regard to depressive symptoms in Parkinson’s disease. We further refine the findings, looking at correlation of genetic signals for clinical depression and Parkinson’s disease, as well as comparing the cell types of the midbrain implicated in each.

Emma Jones

Global unbiased proteomic identification of integral membrane proteins that require Retromer for their endosomal sorting in neuronal systems

The efficient transport of membrane proteins such as signalling receptors and ion channels through the endosomal network is essential for maintaining function of all cells and organelles. The role of this system in neuronal cells appears especially critical with proper function shown to be neuroprotective. Functional deficiency of the evolutionarily conserved Retromer complex, a key regulator of sorting through the endosomal network, has been implicated in a number of neurodegenerative diseases including Alzheimer’s and Parkinson’s diseases. However to understand the role of Retromer in neuroprotection, it is essential that we obtain a detailed understanding of the global array of cargo proteins that rely on this complex for efficient transport.

To address this question and gain a global and unbiased view of the role of Retromer in neuronal function we have used a proteomics-based approach to identify integral membrane proteins whose recycling to the plasma membrane is mediated by Retromer and two associated cargo adaptors, sorting nexin 3 (SNX3) and sorting nexin 27 (SNX27), in primary rat cortical neurons and immortalised human H4 neuroglioma cells. From these approaches we have identified a number of cargo that require the SNX3- and SNX27-Retromer complexes for endosomal recycling, including proteins involved in regulation of synapse organisation (e.g. synaptic adhesion molecule LRFN2, neuronal guidance molecule ephrin B2), chemical synaptic signalling (e.g. GABA and glutamate receptor subunits, calcium regulator STIM1) and solute transport (e.g. human copper transporter SLC31A1). Many of the identified Retromer cargo proteins also have defined links to neuroprotection and dysregulation in neurodegenerative disease.

Our study highlights multiple novel Retromer cargoes across two distinct sub-complexes, providing further insight into the mechanistic basis of Retromer deficiency in neurodegeneration.

Nicole Thomas

Community and Public Health Approaches to Dementia: The ComPHAD Project

The ComPHAD project addresses a critical gap in dementia research by attempting to develop a sustainable methodology to understand the prevalence of dementia within marginalised populations consistently missing from standard health data. This lightning talk provides an overview of the project so far, focusing on its innovative approach, challenges, and collaborative methods to determine what is possible, using a critical realist approach.

Marginalised groups have long been underrepresented in dementia research, leading to a skewed understanding of the disease's prevalence and impact. Several issues exist, such as, low response rates and high attrition rates in observational studies over time, cultural and social inappropriateness of standard diagnostic questions when applied to these groups leading to high false positive results, as well skewed findings from GP health data representative of a whiter population who have been fortunate to achieve a higher educational level. Additionally, linguistic, spiritual and conceptual disparities pose challenges, as many languages lack direct translations for terms like "dementia," potentially leading to misconceptions about the disease.

At the heart of the ComPHAD project is the collaborative co-development of a platform using vignettes. These vignettes have been constructed through scoping reviews, analysis of the grey literature, expert consultations, and engagement with individuals with lived experience. We aim to capture the diverse cultural contexts and language nuances that traditional assessments overlook through a series of workshops. The project leverages a participatory approach, ensuring that the voices of marginalised communities and stakeholders are central in shaping the methodology, including using the Patient Experience Library which is a repository of over 60k published documents relating to PPIE commissioned by charities, NHS Trusts and government bodies.

Jennifer Imm

A role for epigenetic mechanisms in the Lewy body dementias

The Lewy body diseases (LBDs) (Dementia with Lewy bodies (DLB), Parkinson’s disease (PD) and Parkinson’s disease dementia (PDD)) are all neurodegenerative diseases classified by the accumulation of alpha-synuclein in neurons, forming Lewy bodies (LB). We hypothesise that these LBs cause epigenetic changes within neurons and surrounding cells and that these changes can be used to distinguish the different diseases from one another.

DNA and RNA has been extracted from 921 bulk tissue samples from 474 unique donors and, where possible, we have tried to obtain both the cingulate gyrus and prefrontal cortex from the same individual. We have profiled all 921 DNA samples on the Illumina EPIC array, which generates a quantitative measure of DNA methylation for over 850,000 CpG sites. Linear regression and groupwise comparisons were then used to identify loci that are significantly associated with neuropathology or clinical diagnosis.

We have identified significant changes in DNA methylation associated with both clinical diagnosis and neuropathology. These loci include genes that have been previously associated with synucleinopathies, including PTPRN2, DGKI and SYN3.

Processing of samples for fluorescence activated nuclei sorting and laser capture microdissection has begun (n=20/group) to assess the cell-type specificity of the methylation changes.

Brier A. Rigby Dames

Dogs and cats share features of Alzheimer’s neuropathology with humans

Dogs and cats age in ways that are comparable to humans. Similar to humans, cats have an extended lifespan compared to the rest of their genus. Also, these companion animals share many of the same diseases as humans, such as obesity, heart disease, and diabetes, all of which are risk factors for dementia. Both cats and dogs show signs of brain atrophy and cognitive decline with age. In humans, Alzheimer's disease is the most common form of dementia. However, in companion animals, these dementia-type symptoms are typically diagnosed as cognitive dysfunction syndrome or, more specifically, in dogs, canine cognitive dysfunction. Nonetheless, these disease presentations share many commonalities with Alzheimer's disease in terms of changes in behaviour and neuropathology. The two hallmarks of Alzheimer's neuropathology are amyloid-beta (Aβ) plaques and neurofibrillary tangles (NFTs). Elderly dogs share these two hallmark pathologies of Alzheimer's disease with humans: NFTs and classic cored Aβ plaques. While cats may also display tangles in their brain in later life, their Aβ deposits tend to be more diffuse and without the condensed core typically seen in the classic plaques observed in Alzheimer's disease. Collectively, these findings highlight the utility of these companion animals as model systems of human ageing. Furthermore, adopting a One Health perspective, for these species that live in such close proximity to us, could enhance both human and companion animal health research.