BRAIN AGEING

TIME: 11.30 – 12.30

LOCATION: SWAN ROOM

ASTROCYTE-INDUCED DNA DAMAGE AS A MECHANISM OF MOTOR NEURON DEATH IN AMYOTROPHIC LATERAL SCLEROSIS

Jannigje Kok, Sheffield Institute of Translational Neuroscience, University of Sheffield

The cause of motor neuron degeneration in amyotrophic lateral sclerosis (ALS) has long remained unclear. ALS astrocytes have been well established to be toxic to motor neurons, and several studies have shown that DNA damage is a consistent feature in ALS. Preliminary data from the Ferraiuolo lab showed that C9ORF72 ALS astrocytes could induce DNA damage in healthy mouse motor neurons. It was thus hypothesised that astrocyte-induced DNA damage could contribute to motor neuron death in ALS. To test this hypothesis, induced astrocytes (iAstrocytes), which retain epigenetic hallmarks of ageing, were obtained from sporadic ALS, C9ORF72-ALS and SOD1-ALS patients and the conditioned media was used to treat healthy human iPSC-derived motor neurons. It was found that conditioned media from C9ORF72-ALS and one sALS iAstrocyte line could induce increased DNA damage response activation in treated motor neurons within 24 hours, and within 72 hours for remaining ALS iAstrocyte lines tested. This effect was specific to motor neurons, as treating GABAergic neurons with ALS iAstrocyte conditioned media could not induce DNA damage response activation within 24 hours. GABAergic neurons, however, displayed markers of DNA damage response within 72 hours, indicating that they might be more resilient, but not totally spared. The cause of astrocyte-induced DNA damage remains unclear, but preventing astrocyte-induced DNA damage or modulating the motor neuron response to DNA damage could provide potential therapeutic targets.

Β-AMYLOID FIBRIL POLYMORPHISM IN ALZHEIMER'S DISEASE: DOES THE MOLECULAR STRUCTURE OF FIBRILS LEAD TO DIFFERENCES IN THE IMMUNE RESPONSE?

Madeleine Brown, School of Molecular and Cellular Biology, University of Leeds

Alzheimer's disease (AD) is the most common form of dementia, affecting a sixth of the population over 80, and current treatments are only capable of temporarily alleviating symptoms. One of the main pathological hallmarks of AD is the presence of extracellular senile plaques consisting primarily of β-amyloid (Aβ). Aβ fibrils share a characteristic cross-β structure, however structural models for Aβ fibrils have revealed polymorphism at a molecular level *in vitro* and there is evidence that distinct structural variants could be linked to the presentation of different subtypes of Alzheimer's disease.

Working at the interface between structural and cellular biology, this research is investigating differences in the cellular responses to these different fibril structures. With neuroinflammation being another major hallmark of AD, our research focuses specifically on the effects of fibril polymorphs on immune cells. Results have identified differences in the toxicity of different fibril structures towards microglial cells, as well as the efficiency of fibril clearance by these cells. Next steps aim to identify the degree of immune cell activation elicited in response to different Aβ fibril polymorphs, and thus their contribution to neuroinflammation. Differences identified between these fibrils could help to explain the huge amount of variability in symptoms and disease severity that exists between Alzheimer's patients.

UTILISING STRUCTURAL BRAIN IMAGING AND WEARABLE TECHNOLOGY TO UNDERSTAND REAL-WORLD GAIT IMPAIRMENT IN PARKINSON'S DISEASE

Harpreet Chaggar, Institute of Neuroscience, Newcastle University

BACKGROUND: Gait impairment is a cardinal feature of Parkinson's disease (PD) leading to falls. Neural mechanisms underlying gait are poorly understood, limiting therapeutic management. Subcortical structures are areas of both motor control and PD neurodegeneration; the mapping of specific subcortical neural-gait correlates is required to understand gait mechanisms. No group has assessed neural-gait correlates from gait characteristics (e.g. step velocity, step length) measured in the real-world through wearable technology ('wearables'). These better reflect everyday walking compared to gait assessed in a laboratory.

AIM: Map discrete real-world gait characteristics to subcortical brain volumes in PD.

METHODS: PD patients (n=36) two years post-diagnosis and healthy older adults (OA) (n=22) from the ICICLE-PD and ICICLE-GAIT studies had gait continuously monitored at home for seven days using wearables. Volumes of subcortical structures, total intracranial volume corrected, were calculated from T1-weighted MRI scans through FreeSurfer software. Age and sex-adjusted ANCOVAs compared gait and imaging variables between groups. Partial correlations assessed associations between gait characteristics and subcortical brain volumes.

RESULTS: Right hippocampus was significantly smaller in PD compared to OA ($p=0.018$). PD patients had significantly worse gait in 3/7 selected gait characteristics. In OA, the basal ganglia (BG) showed strong partial correlations with gait; in PD, strong correlations were instead found in the cerebellum and hippocampus.

CONCLUSION: Differing neural correlates between PD and OA suggest brain areas compensate for neurodegeneration to maintain real-world gait performance in early disease. Real-world neural-gait correlates are an important next step in understanding gait to improve future therapies

FUNCTIONAL CONNECTIVITY PREDICTS VISUAL HALLUCINATIONS IN DEMENTIA WITH LEWY BODIES

Ramtin Mehraram, Institute of Neuroscience, Newcastle University

Background: The physiological causes of visual hallucinations (VHs) in dementia with Lewy bodies (DLB) are still questioned, as this symptom does not develop in all patients. Previous studies based on electroencephalography (EEG) have found disrupted functional network architecture and reduced dominant power frequency (DF) over the occipital cortex. In this pilot study we investigated whether the functional cortical network alterations in DLB predict DF decrease and the hallucinating condition.

Methods: Resting state EEG signals (128 channels) and magnetic resonance imaging were recorded from 14 healthy controls and 17 DLB participants (eight without VHs). EEG time series were filtered (bandpass: 8-13 Hz), and cortical sources were estimated with sLORETA (Destrieux atlas). Connectivity was measured with weighted phase lag index (WPLI), and assessed with Network Based Statistics. DF was obtained with wavelet transform. The NPI questionnaire was collected from all participants. Spearman's correlations were tested between WPLI of affected connections and the VH score as well as DF. Prediction accuracy was tested with random forest method.

Results and Conclusions: DLB patients showed a significant weakened network cluster over the right hemisphere, disrupted connections along the ventral pathways as well as affected inter-hemispheric links. Reduced WPLI significantly correlated with DF ($\rho=0.59$. $p=0.006$) and the NPI-hallucination score ($\rho=-0.55$, $p=0.01$). The WPLI discriminated the VH condition with accuracy of 76.64% ± 21.15%, and predicted DF values with accuracy of 85%. These results support EEG as a suitable biomarker for diagnosing DLB and assessing the severity of the pathology.