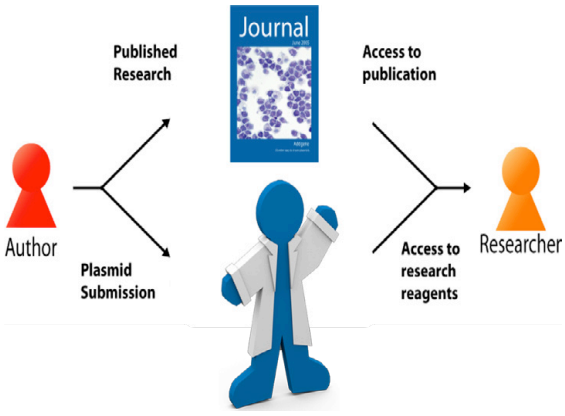
QUEEN SQUARE SYMPOSIUM 2018

19th Annual Queen Square Symposium
Institute of Neurology, Institute of Cognitive Neuroscience

Tuesday 29th of May 2018

addgene

The nonprofit plasmid repository



Addgene is a global, nonprofit repository that was created to help scientists share plasmids. When scientists publish research papers, they deposit their associated plasmids at Addgene and we take care of the quality control, MTA compliance, shipping, and record-keeping.

For scientists looking to use plasmids, Addgene provides a searchable database of high-quality plasmids, pooled libraries, and plasmid kits, available at affordable prices. All plasmids in Addgene's repository are sequenced for quality control purposes. As of 2016, Addgene also provides ready-to-use AAV and lentivirus preparations as a service to scientists.

If you are interested in depositing plasmids at Addgene or if you'd like to learn more about Addgene's collection, please contact **help@addgene.org**

QUEEN SQUARE SYMPOSIUM 2018

7 QUEEN SQUARE

9:00 - 9:30 **Registration**
9:30 - 13:00 **Poster sessions**

33 QUEEN SQUARE

13:00 - 14:00 **Lunch (included)**

14:00 - 14:50 **Dr Selina Wray**
Human stem cell models of Frontotemporal Dementia and Alzheimer's disease

14:50 - 15:20 **PhD talks**
Eleanora Lugara: Acute reduction of the Extracellular Trans-Synaptic Protein LGI1 increases network excitability

Caroline Casey: Huntington's disease phenotypes and disrupted corticostriatal connectivity observed in a novel human iPSC-derived in vitro co-culture model.

15:20 - 15:50 **Coffee break**
15:50 - 16:20 **PhD talks**
Sean Cavanagh: Reconciling persistent and dynamic hypotheses of working memory coding in prefrontal cortex

Lauren Byrne: Parallel evaluation of mutant huntingtin and neurofilament light as biomarkers for Huntington's disease: the HD-CSF study

16:20 - 16:30 **Proteintech**

16:30 - 17:20 **Professor Karl Friston**
Active inference and artificial curiosity

17:20 - 17:30 **Prizes**
17:30 **Drinks reception**

Poster Sessions – 7QS

Session 1 (9:30 – 10:20)

Session 2 (10:30 – 11:20)

Session 3 (11:30 – 12:20)

Finalist Session (12:30 – 13:00)

Session 1 (9:30 – 10:20)

Room 1: Downstairs cluster room

Poster number	Name	Title
1	William De Doncker	Feel the force: Neurophysiological correlates of sensory attenuation
2	Benjamin Chew	Endogenous Fluctuations in the Dopaminergic Midbrain Modulate Drive Choice Variability
3	Francisco Sacadura	"Thermal grill" model of human pain perception facilitates late but not early somatosensory evoked potentials
4	Andrea Castegnaro	Testing of navigation in pre-dementia Alzheimer's disease using immersive virtual reality
5	Leanne Hockey	Attention and inhibition in Tourette's syndrome
6	Laura Monroy	Contribution of Speechreading and Fingerspelling to Reading in Deaf people.
7	Dorothea Hammerer	Using pupillometry and imaging to probe the structure and function of the ageing central noradrenergic system
8	Alexandra Hopkins	High Fear of Negative Evaluation is associated with Biased Learning from Negative Information about the Self
9	Ioannis Sarigiannidis	Induced anxiety makes time pass quicker
10	Ishita Chowdhury	Metacognition and cognitive offloading of delayed intentions in Autistic Spectrum Condition

Session 1 (9:30 – 10:20)

Room 2: Upstairs cluster room

Poster number	Name	Title
11	Benjamin Clarke	Region specific glial stress responses: implications for ALS
12	Steven J. Jerjian	Spinal modulation during action observation
13	Verna Sarajarvi	Do diverse Charcot-Marie-Tooth disease-causing mutations show convergent disease pathomechanisms? Investigation of mitochondrial dysfunction in CMT
14	Martha McLaughlin	Investigating Optogenetic Stimulation of Stem Cell Derived Motor Neurons for Peripheral Neural Replacement in Forelimb Muscles
15	Samuel Hewitt	Inner retinal layer thinning as a biomarker for dementia risk in Parkinson's Disease.
16	Anna Zeitlberger	The identification of potential plasma biomarkers in Friedreich's ataxia
17	Nourelhoda Haridy	Novel homozygous missense variant in HSD17B4 identified in an Egyptian female with Perrault syndrome type II.
18	Merel van der Thiel	Cognitive decline and brain atrophy in the progression of young-onset Alzheimer's disease
19	Seda Sacu	Neural Hyperexcitability within Default-mode Network in patients with Young-onset Alzheimer's Disease
20	Modinat Liadi	Clinical relevance of improving the viability of OECs from the olfactory bulb and mucosa for cell transplantation
21	Manuela Tan	Genetic determinants of motor and cognitive progression in Parkinson's disease
22	Marion Durteste	Investigating the impact of GBA mutations on visual cognitive function in Parkinson's disease
23	Megan Docksey	Influence of NREM parasomnia on daytime functioning, sleep quality, psychological health and quality of life in patients and bed partners.

Session 2 (10:30 – 11:20)

Room 1: Downstairs cluster room

Poster number	Name	Title
1	Alisa Loosen	The influence of subjective confidence on post-decision evidence integration and changes of mind
2	Rachel Bedder	A Computational Model of Mood and Future Prospects
3	Andrew J Watson	Cognitive Subtypes in First-Episode Psychosis: An Empirical Longitudinal Study of Relationship to Cognitive, Symptom and Functional Outcomes.
4		
5	Andreas Flores Martin	The Cognitive Profile of Superficial Siderosis
6	Maximilian Scheuplein	Self-development during adolescence: Is mentalising associated with self-knowledge?
7	Rebecca Settle	Cognitive Mechanisms of Contextual Fear Conditioning
8	Ewa Zotow	Behavioural evidence for pattern separation in human episodic memory
9	Elizabeth Worster	The relationship between visual speech, phonological awareness and reading in hearing children.
10	Ceci Qing Cai	The processing of laughter in people with autism

Session 2 (10:30 – 11:20)

Room 2: Upstairs cluster room

Poster number	Name	Title
11	Veronica Chan	Social cognition outcomes following Traumatic Brain Injury
12		
13	Yumeya Yamamori	The effects of cannabidiol on emotional processing and anxiety: a systematic review
14	Emily Upton	'Tablet-based auditory comprehension therapy after stroke: are items learnt as part of a phrase or as a single lexical unit?'
15	Elias Papadopoulos	Assessing the Preparedness of Patients with Functional Neurological Symptoms after undergoing Preparatory Therapy using Psychometric Evaluation Scales
16	Jeffrey Bergman	Tractography-informed resting-state fMRI segmentation of the thalamus for improved deep brain stimulation targeting in essential tremor
17	Xixi Yang	A cross-sectional exploratory magnetic resonance imaging study evaluating white matter diffusion measures for the overactive bladder in Multiple Sclerosis
18	Olga Tyurikova	Monitoring single-synapse presynaptic calcium dynamics in a mouse model of migraine
19	Mohammed Patel	Differentiating tumour progression from benign treatment effects of stereotactic radiosurgery in patients with cerebral metastases
20	Lorenzo Caciagli	Abnormal hippocampal structure and function in patients with Juvenile Myoclonic Epilepsy and unaffected siblings: a magnetic resonance imaging study
21	Francesca Talami	Simultaneous intracranial EEG-fMRI in a word-generation task
22	Amirah Alsaedi	Systematic Review and Meta-analysis: Arterial Spin Labelling (ASL) Efficiency in Adults Glioma Grading
23	Harith Akram	Towards Connectomic Functional Neurosurgery
24	Lesley Wu	Improving separation of the amygdala and the hippocampus on MRI from an automated parcellation (GIF): application on a FTD cohort

Session 3 (11:30 – 12:20)

Room 1: Downstairs cluster room

Poster number	Name	Title
1	Iqra Nazish	Investigation of the role of LRRK2 in murine macrophage RAW264.7 cells
2	Amy Patel	Pathological, neuroradiological and clinical correlates of B-lymphocytes in multiple sclerosis
3	Beatrice Costa	Frontotemporal dementia: in depth characterization of C9orf72 expansion prevalence in FTD subtypes and bioinformatics analysis
4	Emma Augustin	Patient-derived stem cell models of familial British dementia.
5	Clara Zourray	*In vivo* CRISPR-editing to treat dominant negative mutations causing neurological diseases
6	Berkiye Sonustun	Analysis of α-synuclein post-translational modifications in Idiopathic Parkinson's Disease and Multiple System Atrophy
7	Bimali Hapuarachchi	A cell model for the study of the association of *EIF2AK3*/PERK with PSP
8	Caroline S Casey	Huntington's disease phenotypes and disrupted corticostriatal connectivity observed in a novel human iPSC-derived *in vitro* co-culture model.
9	Ben O'Callaghan	*In vitro* modelling of mitochondrial disease using human induced pluripotent stem cell (hIPSC) derived myotubes harbouring mtDNA mutations
10	Lauren Gittings	Heterogeneous nuclear ribonucleoprotein R in frontotemporal lobar degeneration

Session 3 (11:30 – 12:20)

Room 2: Upstairs cluster room

Poster number	Name	Title
11	Emily Abel	Developing biomarker assays for progranulin and progranulin-related proteins in frontotemporal dementia.
12	Yi Hua Low	The profile of hnRNP K in Alzheimer's Disease
13	Ashvini Keshavan	Stability of blood-based biomarkers of Alzheimer's disease over multiple freeze-thaw cycles
14	GraceORegan	Investigating the role of the innate immune system in HD
15	Lauren M Byrne	Parallel evaluation of mutant huntingtin and neurofilament light as biomarkers for Huntington's disease: the HD-CSF study
16	Viorica Chelban	*NKX6-2* mutations lead to a new distinct disease with spastic ataxia and hypomyelination
17	Roisin Sullivan	Novel loss-of-function mutation in *ACBD5* found in family with ataxia
18	Alaa M. Khan	Genetic investigation of peripheral neuropathy and related disorders using next generation sequencing.
19	Yichen Qiu	'GeneLoop': gene therapy activated by seizures to treat epilepsy
20	Eleonora Lugara	Acute reduction of the Extracellular Trans-Synaptic Protein LGI1 increases network excitability
21	Jana Heneine	Investigating the pathogenic mechanisms of KCNC1-based progressive myoclonic epilepsy
22	Mikail Weston	Chemogenetic dissection of the mechanisms of secondary epileptogenesis
23	Hamad Khan	How bodily physiological signals influence cortical excitability

Session 1(9:30 – 10:20)

S1-P01

Title: Feel the force: Neurophysiological correlates of sensory attenuation

De Doncker W[1], Ondobakka S[1], Kuppuswamy

[1]*Sobell Department of Motor Neuroscience and Movement Disorders, UCL Institute of Neurology*

Background: Attenuation of anticipated sensory input (sensory attenuation) is thought of as being linked to perceived effort. A perceptual consequence of sensory attenuation is the feeling of effortlessness associated with simple self-generated voluntary actions.

Aims: Identify the neurophysiological correlates of sensory attenuation using electroencephalography (EEG) during performance of a force matching paradigm, an established measure of the phenomenon of sensory attenuation.

Methods: When producing a self-generated force to match a previously experienced external force, under normal circumstances, a higher level of force is produced due to under-estimation of self-generated force. To quantify sensory attenuation, a robot probe will apply pre-determined levels of force randomly over the index finger. The participant then matches the force by pushing on a force transducer. The trials will be controlled for the ability to match forces. EEG will be recorded in conjunction with the force matching paradigm.

Results: All data has been collected and is currently being analyzed.

Conclusion: Are there any neurophysiological correlates of sensory attenuation using this newly developed force matching paradigm in healthy volunteers? If so, can the same task be used be to identify neural correlates of sensory attenuation in fatigued stroke survivors. Since stroke survivors with high fatigue often report that simple tasks require high effort, therefore impaired sensory attenuation may underlie high effort.

S1-P02

Title: Endogenous Fluctuations in the Dopaminergic Midbrain Modulate Drive Choice Variability

Chew B[1,2*], Hauser TU[1,2,*], Papoutsi M[2,3], Magerkurth J[2], Dolan RJ[1,2], Rutledge RB[1,2]

** These authors contributed equally to this work.*

[1]Max Planck UCL Centre for Computational Psychiatry and Ageing Research, UCL,[2]Wellcome Centre for Human Neuroimaging, UCL, [3]Huntington's Disease Centre, UCL

Background: Deficits in the dopaminergic reward pathways have been associated with gambling addiction as well as other psychiatric disorders where patients often co-present with problem gambling, such as Attention Deficit Hyperactivity Disorder (ADHD). While pharmacologically boosting dopamine increases risk-taking behavior, little is understood about whether endogenous fluctuations in dopaminergic brain areas can lead to momentary impulses that similarly influence choice behavior.

Aims: To investigate the effect of intrinsic fluctuations in the substantia nigra and ventral tegmental area (SN/VTA) complex on risk-taking behavior.

Methods: We used real-time functional Magnetic Resonance Imaging (rtfMRI), combined with an individually calibrated probabilistic gambling task, to probe whether changes in baseline levels of BOLD (Blood Oxygenation Level-Dependent) activity in the SN/VTA predict subsequent risk-taking behavior in 43 participants. Use of rtfMRI here allowed us precise control over trial presentation across conditions.

Results: When SN/VTA activity was low, participants exhibited greater risk-taking behavior ($t42 = 3.76$, $p < 0.001$), and were also slower to make a decision ($t42 = 3.22$, $p = 0.003$). Computational modelling revealed that the difference in risk-taking between conditions was driven by an increased bias to gamble for any option presented, as opposed to a change in individual utility functions.

Conclusion: Our results suggest that endogenous fluctuations in SN/VTA BOLD activity modulate choice behavior, consistent with the possibility that low intrinsic dopamine may underlie impulsive behaviors in related psychiatric disorders.

S1-P03

Title: "Thermal grill" model of human pain perception facilitates late but not early somatosensory evoked potentials

Sacadura F[1], Brookes T[2], Beck B[3], Fardo F[3,4], Haggard P[3]

[1]Faculty of Life Sciences, Division of Biosciences, UCL, [2]Faculty of Medical Sciences, Division of Medicine, UCL, [3]Insitute of Cognitive Neuroscience, UCL, [4]Danish Pain Research Centre, Aarhus University, Denmark

Background: The thermal grill illusion (TGI) involves a paradoxical burning heat sensation evoked by alternating non-noxious warm and cold temperatures. The TGI has been proposed as an experimental model of chronic pain in humans. Reduced intracortical inhibition has been reported in chronic pain patients.

Aims: We therefore combined TGI conditioning with double-digit electrical stimulation to investigate whether TGI affects somatosensory-evoked potentials (SEPs), and measures of intracortical inhibition based on under-additivity of responses to double-digit stimulation.

Methods: 32 participants received electrical stimulation to the right index, middle or both fingers simultaneously, during four thermal stimulation conditions: warm index/cold middle (TGI), warm/neutral, neutral/cold or neutral/neutral. Importantly, thermal and electrical stimuli were adjusted according to individual pain and detection thresholds. To measure TGI, participants adjusted the temperature of a further stimulus to match the perceived temperature of the target right middle finger.

Results: We found significant temperature overestimation of the cold stimulus when paired with a warm stimulus, confirming TGI. We found no thermal effects on intracortical inhibition in early sensory SEP components (N20, P27, N33, P45, N80). However, thermal stimulation modulated later cognitive SEP components (P100, N140). Specifically, TGI conditioning increased N140 amplitudes to individual finger stimulation, but not double-digit stimulation.

Conclusions: Our results suggest TGI conditioning increases the gain of later, "attentional" somatosensory processing, and also increases intracortical inhibition.

S1-P04

Title: Testing of navigation in pre-dementia Alzheimer's disease using immersive virtual reality

Castegnaro A[1], Howett D[2], King J[3], Chan D[2], Burgess N[1]

[1]Institute of Cognitive Neuroscience, UCL, [2]Department of Clinical Neuroscience, University of Cambridge, [3]Division of Education and Health Psychology, UCL

Background: Alzheimer's disease (AD) is listed as a major public health priority by the World Health Organization. Given the absence of any existing cure, early detection of the disease is a critical focus for the research community. The entorhinal cortex (EC) is one of the first cortical regions to exhibit neurodegeneration associated with AD, such that tests of EC dysfunction are a suitable candidate for early detection. There is a considerable evidence suggesting that the EC is involved in path integration (PI).

Aims: To develop a PI task using immersive virtual reality (iVR) equipment to test the hypothesis that PI is impaired in pre-dementia AD.

Methods: Populations of young healthy participants (n=30), patients with mild cognitive impairment (MCI, n = 45), and age-matched controls (n=30) each completed a PI task. Where available MCI were stratified as having positive (MCI+, n=11) or negative (MCI-, n=14) biomarkers. The PI task consists of participants sequentially walking along an L-shaped outbound path before being asked to return to their starting location.

Results: VR testing was well tolerated by participants. MCI patients exhibit larger errors beyond aging effects. MCI+ patients exhibit significantly larger errors than MCI- patients. The PI task offer a higher classification accuracy compared to several neuropsychological test sensitive to early AD.

Conclusion: MCI patients were impaired in the VR task. The test has been proven to differentiate the MCI patients with and without underlying AD. The test can potentially offer a non-invasive, low-cost, improved diagnosis of pre-dementia AD.

S1-P05

Title: Attention and inhibition in Tourette's syndrome

Hockey LN[1], Haggard P[2], Ganos G[3], Rothwell J[1] & Joyce EM[1]

[1]Sobell Department of Motor Neuroscience, Institute of Neurology, UCL, [2]Institute of Cognitive Neuroscience, UCL, [3]Department of Neurology, Charité, University Medicine Berlin, Germany

Background: Disrupted inhibitory processing may explain why people with Tourette's syndrome (TS) have difficulty with tic control. As tics can be distractable, impaired attentional mechanisms may also play a role.

Aims: To investigate attention and inhibition at the behavioural and neurophysiological level in those with TS. Methods: healthy volunteers and adults with TS underwent CANTAB cognitive testing to assess inhibitory control and attention; a test of interoceptive awareness (IA) (heartbeat mental tracking); and paired pulse transcranial magnetic stimulation (TMS) short-interval intracortical inhibition (SICI) and short afferent inhibition (SAI) to assess inhibitory neurophysiology.

Results: In TS, significant reductions were found for IA, SICI (3ms) and SAI (all time points corresponding to N20 somatosensory evoked potential). There were no significant differences on CANTAB tasks of sustained attention, planning and spatial working memory. On the Intra Extra Dimensional task, a test of rule acquisition and reversal, TS showed a specific impairment in shifting attention to a novel stimulus dimension that was previously incorrect, as indicated by significantly more extradimensional shift errors. In the Stop Signal Reaction Time (SSRT) Task, testing inhibition of a planned response, the SSRT during the last half of the task was significantly longer.

Conclusion: Deficits in cortical inhibition and inhibiting an already activated motor response were found. Impairments in switching attention in order to suppress inappropriate, habitual responses and inaccurately attending to internal autonomic events were also shown. Together impaired inhibition and attention may explain the difficulty in tic control.

S1-P06

Title: Contribution of Speechreading and Fingerspelling to Reading in Deaf people.

Monroy L[1,3], Guiérrez-Sigut E[1,2,3], MacSweeney M[1,3]

[1]Deafness, Cognition & Language Research Centre, UCL, [2]Departamento de metodología y ciencias del comportamiento, Universidad de Valencia, [3]Institute of Cognitive Neuroscience, UCL.

Background: It has been reported that the majority of deaf children perform poorly in reading tasks compared to their hearing peers (Lederberg, et al., 2013). A poor use of phonological information during word recognition has been suggested as one of the factors of this poor reading development (Perfetti & Sandak, 2000), although they might make an efficient use of orthographic information (Bélanger & Rayner, 2015). Speechreading and fingerspelling abilities are thought to aid access the creation of a more complete phonological representation of the spoken language (Mohammed et al., 2006; Haptonstall-Nykaza & Schick; 2007), hence facilitating access to written words.

Aims: The aims of this study were to examine how phonological and orthographic information is used during word recognition by a group of 73 deaf teenagers (n=53, Age=12-20) and adults (n=20, Age=21-61) reading in Spanish. Additionally, whether the use of this information is related to their speechreading and fingerspelling skills.

Methods: First, participants performed a lexical decision task over printed target words that were preceded by phonological or orthographically related masked primes (or appropriate controls; Experiments 1 and 2). Second, participants decided whether fingerspelled stimuli were real Spanish words or not. Pseudowords included pseudohomophones and replaced letters items. Third, participants were tested in reading, speechreading and fingerspeling abilities amongst other tests.

Results and Conclusion: We predict that a larger phonological effect for the on-line tasks would be positively correlated with better reading, speechreading and fingerspelling abilities. Whether this relationship will be found for orthographic effects is an open question.

S1-P07

Title: Using pupillometry and imaging to probe the structure and function of the ageing central noradrenergic system

Liu, K.[1], Loane, C.[2], Callaghan M.F.[3], Howard, R.J.[1], Düzel, E.[2,4,5], & Hämmerer, D.[2,4,5]
[1]Division of Psychiatry, UCL,[2]Institute of Cognitive Neuroscience, UCL, [3]Wellcome Centre for Human Neuroimaging, UCL Institute of Neurology,[4]German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany, [5]Institute of Cognitive Neurology and Dementia Research, Otto-von-Guericke-University Magdeburg, Magdeburg, Germany

Background and Aims: Neuronal loss in noradrenergic (NA) structures of the brain stem (Locus Coeruleus, LC and its projections) during ageing is of comparable scale to the neuronal loss seen in dopaminergic nuclei. Animal and human pharmacological studies show that noradrenergic modulation supports a wide range of higher cognitive functions, including memory encoding, selective attention, and cognitive flexibility. However, we don't know yet to what extent altered LC function and consequent altered NA modulation with ageing impacts cognitive function.

Methods: We present results from studies which investigate the relevance of age differences in LC structure and function for adult age differences in emotional memory, using novel in vivo structural MRI measures and pupillometry (pupil dilation can serve as a proxy measure for functional LC responses).

Results: Pupillometric data indicate a reduced responsiveness of the ageing NA system during memory encoding. Likewise, structural LC studies suggest reduced LC integrity in older adults and that this likely contributes to impaired memory performance with increasing age. Further pupillometric data implicates the NA system also in executive control of response inhibition.

Conclusions: Our data suggest a reduced functionality of the central noradrenergic system in ageing. The observed link between an in vivo assessment of LC integrity and cognitive performance opens new possibilities for exploring the role of this structure in healthy ageing and dementia, as the LC is one of the first structures to show neuropathology in Alzheimer's disease and exhibits substantial neuronal loss as the disease progresses.

S1-P08

Title: High Fear of Negative Evaluation is associated with Biased Learning from Negative Information about the Self

Hopkins A[1,2], Dolan R[1,2], Button K[3], Moutoussis M[1,2]

[1]Wellcome Centre for Human Neuroimaging, UCL Institute of Neurology, [2]Max Planck Centre for Computational Psychiatry and Ageing Research, [3]Department of Psychology, Bath University

Background: People who are highly fearful of negative evaluation (FNE) display biased processing of social-evaluative information when related to the self. They select fewer positive words when asked to predict how another agent would describe them, but display no bias when making predictions about an unknown other agent.

Aims: To investigate the mechanism underlying the negative self-bias in high FNE individuals. **Methods**: Data from a probabilistic social learning task (n=100) completed by participants that varied along a continuum of low to high FNE was modelled using adapted Rescorla-Wagner reinforcement learning models. AIC and BIC were used to select the winning model.

Results: The winning model contained separate learning rates for self-negative and self-positive information but a single learning rate for other information. Individuals higher in FNE had higher learning rates for negative information for the self only.

Conclusion: The updating of information for the self is valence specific, whereas for others is the same across valences. The self-negative processing bias in high FNE individuals is reflected in higher learning from negative information.

S1-P09

Title: Induced anxiety makes time pass quicker

Sarigiannidis I[1], Grillon C, Ernst M, Roiser J[1], Robinson O[1]

[1]Institute Of Cognitive Neuroscience, UCL, [2]Section on Neurobiology of Fear and Anxiety, NIH

Background & aim: Anecdotal and experimental evidence suggest that during unpleasant events, e.g. traumatic incidents such as car accidents, time slows down (i.e. time is overestimated). However aversive events can elicit at least two dissociable subtypes of reactions: fear (transient and relating to an imminent event) and anxiety (diffuse and relating to an unpredictable event). We hypothesised that anxiety might have an opposite effect on time perception compared to fear.

Methods: To test this hypothesis we combined a robust anxiety manipulation (threat-of-shock) with a widely used timing task in which participants judged whether the duration of a stimulus was long or short.

Results: In line with our hypothesis, across three experiments (with varying stimulus timings and shock levels), participants significantly underestimated time under inducted anxiety, as indicated by a rightward shift of the psychophysical function (meta-analytic effect size: d=0.68, 95% confidence interval: 0.42-0.94).

Conclusion: Our results suggest that experimentally inducing anxiety leads to underestimating the duration of temporal intervals, which might help explain different subjective experiences of disorders related to fear (e.g. specific phobias) relative anxiety (e.g. generalised anxiety disorder).

S1-P10

Title: Metacognition and cognitive offloading of delayed intentions in Autistic Spectrum Condition

Chowdhury I[1]

[1]*UCL Institute of Cognitive Neuroscience*

Background: Prospective memory (PM) is the ability to remember a task which has to be done in the future. In real-life people use reminders, i.e. cognitive offloading, to help with their PM. To judge whether or not one requires a reminder, they analyse costs and benefits of reminders. Such an assessment requires one to know their own minds, i.e. metacognition. People with Autism Spectrum Condition (ASC) are thought to have impairments in metacognition, and therefore may not be able to optimally judge the costs and benefits of using reminders in relation to their own PM.

Aims: To investigate if people with ASC are optimal in choosing between using their memory and using reminders (cognitive offloading) based on metacognitive knowledge about their own PM abilities.

Methods: A touchscreen-tablet based delayed-intention paradigm was used to examine PM, metacognition and offloading strategy in 27 highly-functioning ASC and 29 matched TD adults, in the presence of external monitory reward (which was proportional to performance).

Results: ASC performance in unaided PM task and cognitive offloading behaviour was comparable to TD. ASC also showed efficient metacognitive judgement and control.

Conclusion: This suggests that metacognition is not necessarily impaired in ASC and that monitory reward can possibly improve PM performance and strategy-use in ASC.

S1-P11

Title: Region specific glial stress responses: implications for ALS

Clarke B[1], San Gil R[2], Yip J[1], Kalmar B[1], Greensmith L[1]

[1]Sobell Department of Motor Neuroscience & Movement Disorders, UCL Institute of Neurology,[2]Illawarra Health and Medical Research Institute, School of Biological Sciences, University of Wollongong

Background: Non-cell autonomous mechanisms contribute to the pathology of motor neuron disease. Regional variability of motor neuron death between the cortex and the spinal cord may be caused by differences in the stress responses of surrounding glial cells.

Aims: To compare the inflammatory and heat shock responses of cortical and spinal cord glia in the SOD1G93A model of motor neuron disease.

Methods: Primary mixed glial cultures were dissected from SOD1G93A/WT P3 mice and maintained for 12 days in vitro. Cells were treated with inflammatory mediators or were subjected to heat shock at 42°C for 30 minutes. Released NO was measured using Griess assays and immunoblotting was performed to analyse changes in iNOS, pNF-κB and Hsp70.

Results: Spinal cord glia expressed higher levels of NO and iNOS than cortical glia. However, there was no difference in NO or iNOS between WT and SOD1G93A glia. Although there were no regional differences in the expression of Hsp70, this protein was downregulated in both SOD1G93A cortical and spinal glia following exposure to heat stress. Heat stress reduced inflammatory signalling in spinal cord but not cortical glia.

Conclusions: Spinal cord glia are more immunoreactive than cortical glia, possibly accounting for regional differences in damage in ALS. Impairment of the heat shock response in glia may exacerbate inflammatory signalling and subsequent damage observed in the ALS spinal cord.

S1-P12

Title: Spinal modulation during action observation

Jerjian SJ[1], Lemon RN[1], Kraskov A[1]

[1]*Sobell Department of Motor Neuroscience and Movement Disorders*

Background:Observation of grasp elicits activity in macaque motor areas, including pyramidal tract neurons (PTNs) projecting to the spinal cord. Some PTNs suppress firing during observation. The net effect of action observation on spinal circuits is poorly understood.

Aim: To assess spinal motor neuron excitability during action observation.

Methods: One rhesus macaque was trained to perform or observe reach-to-grasp movements on two objects, affording precision grip and whole-hand grasp. On some observation trials, grasp visibility was altered, with a screen going opaque either after experimenter movement onset, or before information related to the upcoming observed grasp was available. Biphasic stimuli were delivered during task performance via electrodes implanted in the left medullary pyramid (300μA, 1.66Hz), and we recorded muscle activity through subcutaneous electrodes in right hand and arm muscles. Stimuli timings were binned relative to multiple task events, and average motor evoked potential (MEP) amplitudes within bins were compared across task epochs and conditions.

Results: During grasp observation, we found a specific facilitation of MEPs relative to baseline in the first dorsal interosseous (1DI) muscle for precision grip. This effect disappeared if grasp was obscured and the target object could not be predicted.

Conclusion: Action observation can produce grasp-specific facilitation of spinal excitability, depending on whether the upcoming grasp can be directly observed or predicted.

S1-P13

Title: Do diverse Charcot-Marie-Tooth disease-causing mutations show convergent disease pathomechanisms? Investigation of mitochondrial dysfunction in CMT

Sarajarvi V[1,2], Kalmar B[1], Fernandes I[1], Reilly MM[2], Greensmith L[1,2]

[1]*Sobell Department of Motor Neuroscience and Movement Disorders,* [2]*MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology*

Background: Charcot-Marie-Tooth (CMT) disease is a group of peripheral neuropathies with over 80 causative genes identified to date. The mutations affect proteins with wide ranging cellular functions including cytoskeletal structure, mitochondrial function, axonal transport and endosomal signalling. Despite the identification of several CMT-causing mutations, the underlying pathomechanisms of disease remain unclear. It is possible that common pathomechanisms may be involved in different forms of CMT, or conversely, there may be great specificity in the cellular changes caused by different mutations.

Aims: In this project we used patient-derived fibroblasts to investigate whether mitochondrial abnormalities are present primarily in CMT caused by mutations in mitochondrial genes, or whether they also manifest in CMT cases caused by mutations in genes that are not directly linked to mitochondria.

Materials and Methods: Fibroblasts from four controls and seven patients with the following CMT-causing mutations were studied: A) Mitochondrial proteins: MFN2, MT-ATP6 and OPA1 (Optic atrophy-causing mutation); B) Non-mitochondrial proteins expressed in fibroblasts: FIG4 and HSPB1; C) Non-mitochondrial proteins not expressed in fibroblasts: NEFL and SH3TC2. We investigated mitochondrial network morphology, protein expression and function in these fibroblasts.

Results: A subset of CMT patient fibroblasts with mitochondrial and non-mitochondrial mutations showed alterations in mitochondrial network morphology, mitochondrial membrane potential and cellular calcium handling.

Conclusion: A subset of CMT-causing mutations cause mitochondrial abnormalities, and these are not isolated to the mitochondrial mutations. Therefore, mitochondrial dysfunction might be a common pathomechanism across different forms of CMT.

S1-P14

Title: Investigating Optogenetic Stimulation of Stem Cell Derived Motor Neurons for Peripheral Neural Replacement in Forelimb Muscles

McLaughlin M[1], Bryson JB, Greensmith L[1]

[1]*Sobell Department of Motor Neuroscience and Movement Disorders, UCL Institute of Neurology*

Background: An exciting novel treatment strategy has recently been proposed for the restoration of motor function after damage or neurodegeneration in the CNS. This strategy involves transplantation of embryonic stem cell derived motor neurons (esMNs) into peripheral nerves to reinnervate specific target muscles. Our group has previously shown that engraftment of esMNs expressing light-sensitive channelrhodopsin, into the denervated sciatic nerve, can restore function to paralysed hindlimb muscles in mice in response to optical stimulation. However, chronic optogenetic stimulation of the esMNs after engraftment may be necessary to optimise this neural replacement strategy, as neural activity is essential for neuromuscular junction formation and maintenance. Additionally, adapting our strategy for reinnervation of rodent forelimb muscles is likely to have greater potential relevant for future clinical translation of this neural replacement strategy, as it would enable restoration of arm and hand function.

Aims: 1.) To investigate the effect of in vitro optogenetic stimulation on esMN neuromuscular junction formation. 2.) To adapt our neural replacement strategy for reinnervation of opposable muscles in mouse forelimb.

Methods: 1.) Co-cultures of esMNs and embryonic stem cell derived muscle fibres will be used to assess neuromuscular junction formation under various patterns of optical stimulation via an in vitro LED array. 2.) As a first step in developing our strategy for reinnervation of forelimb muscles, we will confirm the innervation of select opposable muscles by the radial and median nerves using anterograde tracers, at the level of a potential engraftment site in the axillary region.

Hypotheses / Outcomes: 1.) We predict that chronic optogenetic stimulation will increase successful formation of neuromuscular junctions in our co-cultures. 2.) We will identify the optimal site for engraftment of esMNs for the reinnervation of opposable muscles in the forelimb.

S1-P15

Title: Inner retinal layer thinning as a biomarker for dementia risk in Parkinson's Disease.

Hewitt S[1], Leyland L[2], Mahmood R[2], Durteste M[1], Bremner F[3], Weil RS[2,4]

[1]UCL Institute of Neurology, [2]Dementia Research Centre, UCL Institute of Neurology, [3]Institute of Ophthalmology, UCL, [4]The Wellcome Centre for Human Neuroimaging, UCL Institute of Neurology

Background: Visual dysfunction in Parkinson's disease (PD) is a marker for dementia risk. In the retina, dopamine deficiency impairs neural transmission while a-synuclein deposition occurs within the inner layers. Recent studies using optical coherence tomography (OCT) have found that thickness and volume of inner retinal layers and foveal shape are sensitive structural markers for PD. The relationship between these parameters and PD-dementia risk has not been investigated.

Aims: We include a previously described algorithm to predict risk of cognitive involvement in PD. Our hypothesis is that macular thinning of inner retinal layers differentiates PD patients at risk of dementia (PD-AR), PD at lower risk (PD-N) and controls. This case-control analysis is an initial cohort of a longitudinal study.

Methods: Data will include at least 30 people with PD and 25 age-matched controls. Participants underwent detailed neuropsychology, assessment of PD, ophthalmic examination and OCT.

Results: Retinal nerve fibre layer thinning does not characterise PD at the group level. Measures of inner retinal layers (thickness and volume) are significantly reduced for PD-AR. **Conclusion**: Inner retinal layer thinning may be a useful marker to identify PD patients at risk of dementia. A simple computation of foveal pit gradient could be a feasible clinical tool for trial selection. These findings need to be validated longitudinally.

S1-P16

Title: The identification of potential plasma biomarkers in Friedreich's ataxia

Zeitlberger A[1], Heslegrave AJ[1], Zetterberg H1, Giunti P1

[1]*Department of Molecular Neuroscience, UCL Institute of Neurology*

Background: Friedreich's ataxia (FRDA) is the most prevalent form of autosomal recessive hereditary ataxia worldwide. Disease-modifying treatments are not available yet, however several compounds are currently under investigation in preclinical and clinical trials. The identification of robust and easily accessible biomarkers is paramount to improve clinical trial design.

Aims: To investigate the role total of total tau, neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP) and ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1) as plasma biomarkers in FRDA.

Methods/Materials: Plasma samples and clinical information from 13 healthy controls and 33 patients with genetically confirmed FRDA were prospectively collected. NfL, total tau, GFAP and UCH-L1 levels were measured using the ultrasensitive digital Single Molecule Array (Simoa) technology.

Results: Mean concentrations of plasma NfL and GFAP were significantly higher in FRDA patients than in controls (Mann-Whitney Test, $p<0{\cdot}000$ and $p<0{\cdot}040$). Contrarily, total tau was significantly lower in FRDA patients (Mann-Whitney Test, $p<0{\cdot}030$). GFAP concentrations showed a moderate correlation with the disease duration, however this was not significant (correlation coefficient 0.35, $p = 0{\cdot}078$). Biomarker levels showed no significant correlation with clinical scores in this cohort.

Conclusion: Plasma NfL and GFAP concentrations are raised in FRDA patients compared to age-matched controls, whereas total tau is lower. Their association with disease progression requires further investigation in a larger patient cohort and longitudinal data.

S1-P17

Title: Novel homozygous missense variant in HSD17B4 identified in an Egyptian female with Perrault syndrome type II.

Haridy NA[1,2], Rizig M[1], Vandrovocova J[1], Mamdouh A[2], Hameed MAA[2], Hamed SA[2], Houlden H[1]

[1]Department of Molecular Neuroscience, UCL Institute of Neurology,[2]Department of Neurology and Psychiatry, Assiut University Hospital, Faculty of Medicine, Assiut, Egypt

Background: Perrault syndrome (PS) is a rare autosomal recessive disorder that manifested with sensorineural hearing loss in both sexes and ovarian dysgenesis in females. The syndrome is clinically and genetically heterogeneous. It was classified into two subtypes: Type (I) static and without neurological features and type (II) progressive and with neurological disease. The neurological manifestations included ataxia, peripheral neuropathy and others. Six genes are implicated in causing this syndrome so far. HSD17B4 was the first gene to be linked to this syndrome. HSD17B4 encodes the D-bifunctional protein (DBP) which is essential for the peroxisomal β-oxidation of fatty acid and steroid metabolism.

Aims: To report for the first time an Egyptian female with Perrault syndrome type II.

Patients and Methods: A 30-year-old Egyptian female with ovarian dysgenesis, ataxia, peripheral neuropathy and late onset hearing loss. All common causes of spinocerebellar ataxias were excluded by doing PCR and fragment analysis. Negative finding in our patient leads to using whole exome sequencing that validated by Sanger sequencing.

Results: A novel missense homozygous mutation in HSD17B4 gene (c.689T>C, p.Met230Thr) was identified in the patient with her mother heterozygous. This mutation is predicted to cause a loss of the dehydrogenase enzymatic activity of the DBP protein in a pattern consistent with PS phenotype. The mutation was absent in 200 Egyptian controls.

Conclusion: We proposed the first Egyptian case of Perrault syndrome II with late onset hearing loss. This finding confirms the role of the next-generation sequencing techniques in the diagnosis of such cases.

S1-P18

Title: Cognitive decline and brain atrophy in the progression of young-onset Alzheimer's disease

van der Thiel MM[1,2], Slattery CF[1], Hutel M[1,2], Patterson RW[1], Foulkes AJM[1], MacPherson K[1], Barkhof F[1,2,3,4], Fox NC[1], Schott JM[1]

[1]Dementia Research Centre, UCL Institute of Neurology, [2]Translational Imaging Group, Centre for Medical Image Computing, UCL Department of Medical Physics and Biomedical Engineering, [3]Department of Brain Repair and Rehabilitation, UCL Institute of Neurology, [4]Division of Neuroradiology and Neurophysics, UCL Institute of Neurology

Background: Young-onset Alzheimer's disease (YOAD) refers to Alzheimer's disease with an onset before 65 years of age. The clinical representation of YOAD is heterogeneous, with individuals classified as typical AD (tAD) showing primarily memory impairment and posterior cortical atrophy (PCA)-patients demonstrating parietal dysfunction. Supporting heterogeneity in clinical representation, differential atrophy patterns are observed.

Aims: To investigate cognitive decline and brain volume in tAD(n=16), PCA(n=5) and controls(n=16) using structural MRI and neuropsychological tests.

Methods: Neuropsychological testing and MRI measures were performed at baseline and 1-year follow-up. Whole-brain-, ventricular-, left and right hippocampal volumes were determined per time-point. Brain atrophy was calculated using the boundary shift integral (BSI). One-way ANOVA's with Tukey HSD tested group differences in neuropsychological scores and brain volume at both time points and in BSI.

Results: At baseline, tAD and PCA scored lower at RMT words, digit-span backwards, arithmetic and fluency than controls. At follow-up, both clinical groups scored lower than controls, but only the dot-counting test was able to differentiate between tAD and PCA. PCA performed worse on dot-counting than tAD and declined significantly stronger in score. At baseline, larger ventricular volume was observed in tAD as compared to controls, and in PCA and tAD at follow-up. Interestingly, both clinical groups showed a higher atrophy rate in all but left hippocampal volume for PCA.

Conclusion: The two major clinical subtypes of YOAD differ from controls on brain volume and neuropsychological data. This study identified the dot-counting test as an accurate test.

S1-P19

Title: Neural Hyperexcitability within Default-mode Network in patients with Young-onset Alzheimer's Disease

Sacu S[1,2,a], Slattery CF[3,a], Friston KJ[2], Paterson RW[3],. Foulkes AJM[3], Rees G[2], Fox NC[2], Schott JM[3,b], Razi A[2,4,5,b]

[a]Joint first authors.[b]Joint last authors.[1]Berlin School of Mind and Brain, Humboldt-Universität zu Berlin, Berlin, Germany, [2]Wellcome Centre for Human Neuroimaging, UCL Institute of Neurology, [3]Department of Neurodegenerative Disease, UCL Institute of Neurology, [4]Monash Institute of Cognitive and Clinical Neurosciences & Monash Biomedical Imaging, Monash University, Clayton, Australia, [5]Department of Electronic Engineering, NED University of Engineering and Technology, Karachi, Pakistan

Background: Young-onset Alzheimer's Disease (YOAD) is a rare form of AD which consists of approx. 5% of all AD cases. The functional organization of the large-scale brain networks during rest is far less clear in YOAD compared to more common late-onset AD.

Aim: We aimed to investigate effective connectivity within default-mode network (DMN) in patients with sporadic YOAD using resting state functional MRI (fMRI).

Methods: All participants underwent resting-state fMRI scan. Effective connectivity was calculated using spectral Dynamic Causal Modelling (spDCM). Voxel Based Morphometry (VBM) was performed to define localized gray matter density across the whole brain. All participants underwent Mini Mental State Examination (MMSE).

Results: We identified higher excitatory effective connectivity between DMN nodes in patients with YOAD compared to healthy controls (HCs). In addition, patients with YOAD exhibited lower gray matter density in DMN nodes including posterior cingulate cortex, angular gyrus, hippocampus and had lower scores in MMSE compared to HCs. Patients were further divided into Apoe-4+ and Apoe-4– groups to see the effect of major genetic risk factor on effective connectivity within DMN. We found increased excitatory effective connectivity between DMN nodes in Apoe-4 carriers compared to non-carriers.

Conclusion: These results indicate that neural hyperexcitability within DMN might be a potential biomarker for YOAD and will provide new insight into YOAD pathophysiology.

S1-P20

Title: Clinical relevance of improving the viability of OECs from the olfactory bulb and mucosa for cell transplantation

Modinat Liadi[1]
[1]*Spinal Repair Unit, Brain Repair & Rehabilitation, UCL Institute of Neurology*

Background: Transplantation of olfactory ensheathing cells (OECs) to a lesion site in animal experiments have been shown to aide recovery after spinal cord injury. The first clinical application by our collaborators showed encouraging outcome of axonal regeneration and functional recovery after transplantation of autologous human olfactory bulb OECs (hOECs) to the site of injury with simultaneous bridging of the spinal cord gap with autologous peripheral nerve grafts. However, the clinical application did reveal a limitation of hOECs and OECs generally when treating injuries of large size and cavity. Furthermore the olfactory mucosa still remains the more desirable option for sourcing OECs has it is the less invasive method.

Aim: The aim is to establish methods of expanding the OECs obtained from the olfactory bulb and mucosa.

Methods: OB cell culture: The cells were prepared by dissociation of the olfactory bulbs of adult Sprague-Dawley (SD) rats in trypsin solution. The cells were cultured in medium consisting of Dulbecco's modified Eagle's medium (DMEM)/F12 + 10% foetal bovine serum (FBS) + Penicillin/Streptomycin (100U/ml, 100µg/ml) in PDL coated 2D dishes. A disc-shaped collagen scaffold was made of 250µl of a mixture of 2 x 105 cells with collagen (4.8mg/ml), and cultured for 7 days. The cells were distributed throughout the collagen, differentiated to their typical morphologies and formed contiguous meshwork. The size of the scaffold was around 1cm in diameter and 0.5mm, thickness. OM cell culture: the cells were prepared by dissociation of the olfactory mucosa dissected out from the septum of the rat nasal cavity in collagenase type I solution. The cells were cultured in a medium consisting of Dulbecco's modified Eagle's medium (DMEM)/F12 + 10% foetal bovine serum (FBS) + Penicillin/Streptomycin (100U/ml, 100µg/ml) + 1% Insulin-Transferrin-Selenium in PLL coated 2D dishes. Both cultures were maintained until they became 90% confluent or required end time point. The first change of the medium for OB cells was on the 5th day due to OEC's weak adhering property; 3rd day, OM cells; OM cell culture with modified medium: the OM cells were cultured with the same medium as above supplemented with 0.02% 10µM Forskolin and 1% N2.

Results: OB-OECs grow well in collagen and mixture of OB-OEC with collagen can form 3-dimensional cellular collagen scaffolds. Modification of OM culture increase yield of OECs.

Conclusion: OECs from OB and OM can be increased and expanded.

S1-P21

Title: Genetic determinants of motor and cognitive progression in Parkinson's disease

Tan MMX[1], Hubbard L[2], Pittman A[3], Lawton MA[4], Kanavou S[4], Wood NW[3], Hardy J[3], Ben-Shlomo Y[4], Williams NM[2], Grosset DG[5], Morris HR[1].

[1]Department of Clinical Neuroscience, UCL Institute of Neurology, [2]Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, [3]Department of Molecular Neuroscience, UCL Institute of Neurology, [4]School of Social and Community Medicine, University of Bristol, [5]Institute of Neurological Sciences, Queen Elizabeth University Hospital.

Background: Parkinson's disease (PD) is a progressive neurodegenerative condition for which there are no treatments that stop or slow disease progression. Common genetic variants may contribute to variation in disease progression, and could potentially be targeted for development of new disease-modifying therapies.

Aims: Motor and cognitive progression in Parkinson's is heterogeneous. Our aim is to identify single nucleotide polymorphisms (SNPs) associated with disease progression. **Methods**: 1987 patients with recent-onset PD were recruited to the Tracking Parkinson's study. We conducted Genome Wide Association Studies (GWASs) to identify variants associated with motor and cognitive progression.

Results: Early results from the motor progression GWAS showed that one loci in Chromosome 3 is significantly associated with change in MDS-UPDRS Part III score at 18 months, p<5x10-8. For cognitive progression, no SNPs reached genome-wide significance. However several loci in Chromosome 7, 4 and 11 reached nominal significance. We will take these variants forward for replication in independent cohorts and investigate the biological plausibility of candidate variants.

Conclusion: Our pilot analyses show early evidence that common genetic variants may be associated with motor and cognitive progression but longer follow-up is required.

S1-P22

Title: Investigating the impact of GBA mutations on visual cognitive function in Parkinson's disease

Durteste M[1], Leyland LA[2], Mahmood R[2], Hewitt S[1], Lee K[3], Saygin AP[4], Miller LE[4], Song C[5,6],Toffoli M[3], Mullin S[1,7], Schapira AH[3], Weil RS[2,5]

[1]UCL Institute of Neurology, [2]Dementia Research Centre, UCL Institute of Neurology,[3]Department of Clinical Neurosciences, UCL Institute of Neurology, [4]Department of Cognitive Science, University of California, USA, [5]The Wellcome Centre for Human Neuroimaging, UCL Institute of Neurology, [6]UCL Institute of Cognitive Neuroscience, [7]Institute of Translational and Stratified Medicine, Plymouth University Peninsula School of Medicine

Background: Heterozygous mutations in the glucocerebrosidase gene (GBA) are the most important genetic risk factor for Parkinson's Disease (PD). PD patients carrying a GBA mutation (GBD-PD) show a particularly aggressive disease course with severe cognitive decline that manifests in the form of prominent visuo-perceptual deficits.

Aims: 1) To elucidate the role of GBA mutations on visual cognitive function in PD using a recently developed tool1 (Cats and Dogs test) and two other computerised tasks (Biological Motion and Contrast Sensitivity). 2) To delineate a sensitive marker capable of detecting patterns of pronounced visuospatial deficits for early identification of patients at high risk of carrying a GBA mutation.

Methods: Participants were assessed using three computerised visual tasks and detailed neuropsychology. Data will include four participant groups (n=40): GBA-PD patients, idiopathic PD patients, unaffected GBA carriers, and healthy controls.

Results: Preliminary results indicate that there are significant differences in scores on the Cats and Dogs (p=0.050) and Biological Motion (p=0.038) tests between GBA-PD and GBA-negative patients. No difference was found between GBA carriers and controls.

Conclusion: GBA-PD patients exhibit more severe visual cognitive dysfunction than idiopathic PD patients as assessed by the Cats and Dogs and Biological motion tasks. The latter could constitute sensitive markers for the early identification of GBA-PD patients.

S1-P23

Title: Influence of NREM parasomnia on daytime functioning, sleep quality, psychological health and quality of life in patients and bed partners.

Docksey M, Eriksson S

[1]Department of Clinical and Experimental Epilepsy (DCEE), UCL Institute of Neurology, [2]National Hospital for Neurology and Neurosurgery (NHNN)/UCLH NHS Foundation Trust, [3]Sleep Service, Newcastle upon Tyne Hospitals NHS Foundation Trust, [4]Sleep Disorders Centre, Guy's and St Thomas' NHS Foundation Trust

Background: Non-rapid eye movement (NREM) parasomnias are unwanted night-time events such as sleepwalking, night terrors and sexsomnia, thought to be due to incomplete awakening from deep NREM sleep. Complaints of tiredness and poor sleep are frequently reported in patients, however formal assessments have been limited and bed partners have never been included in analyses.

Aims: To investigate daytime functioning, sleep quality, psychological health and quality of life (QoL) in adults with NREM parasomnia and their bed partners.

Methods: 32 diagnosed NREM patients and 14 bed partners were included. All participants completed questionnaires assessing daytime somnolence, insomnia, sleep quality, depression, anxiety and QoL. Patients completed an additional questionnaire assessing NREM parasomnia characteristics.

Results: Using clinical cut-offs, questionnaire scores revealed poor sleep and insomnia symptoms in patients and bed partners, while daytime somnolence was normal. Both groups showed increased anxiety and reduced QoL, with depression above threshold scores in patients only. Significant associations were found between effects of episodes and decreased sleep quality in patients ($p < 0.05$), and greater frequency with insomnia ($p < 0.005$). Increased episode severity was also significantly associated with poorer sleep in bed partners ($p > 0.001$), insomnia ($p < 0.05$) and reduced QoL ($p < 0.05$).

Conclusion: Adult NREM parasomnia is a condition that negatively affects sleep quality, anxiety and QoL in patients and for the first time also shows an impact on their bed partners. Additionally, increased frequency of episodes are potentially damaging to sleep quality in patients and overall QoL for their bed partners.

S2: Session 2 (10:30 – 11:20)

S2-P01

Title: The influence of subjective confidence on post-decision evidence integration and changes of mind

Loosen AM[1], Rollwage M[2,3], Fleming SM[2]

[1]UCL Institute of Neurology, [2]Wellcome Trust Centre for Neuroimaging, UCL, [3]Max Planck UCL Centre for Computational Psychiatry and Ageing Research

Background: Recent research suggests that confidence in a decision influences subsequent changes of mind. However, task performance and subjective confidence are tightly correlated. As a consequence, isolating and examining the unique impact of confidence on subsequent cognitive processes and behaviour is difficult. A new paradigm enabled us to successfully dissociate the two and to investigate the influence of subjective confidence on changes of mind and post-decision information processing. **Aims**: To investigate the influence of subjective confidence on post-decision evidence integration and changes of mind. **Hypotheses**: High confidence in an initial decision will reduce the sensitivity to post-decision evidence and later changes of mind. **Methods**: We used a psychophysical paradigm (i.e., positive evidence manipulation) to dissociate task performance from subjective confidence. Subjects (N=28) completed a random dot motion task, in which they indicated the direction in which the dots were moving as well as their subjective confidence in their decision. Before making their second and final decision, subjects were presented with additional evidence (i.e., an additional stimulus in which the predominant movement was the same). **Results**: The analysis showed that subjective confidence in an initial decision predicted later changes of mind. When people were highly confident in their first decision, they were less likely to later change their minds. Our manipulation was associated with changes of mind, however, this relationship was mediated by subjective confidence. The interaction between confidence and changes of mind additionally predicted the reaction time in the second decision. We could also see an increase in metacognitive accuracy (i.e., type 2 sensitivity) between the first and second decision, which was moderated by the confidence level in the initial decision. **Conclusion**: High confidence in an initial decision reduces the likelihood of later changes of mind and prolonged reaction times in case that people do change their mind. Furthermore, high confidence results in reduced post-decision evidence processing.

S2-P02

Title: A Computational Model of Mood and Future Prospects

Bedder R[1,2], Blain B[1,2], Lowther E[1,2], Rutledge R[1,2]

[1]Max Planck UCL Centre for Computational Psychiatry and Ageing Research

Background: Our mood is affected not only by what is currently happening, but also what we believe is likely to happen in the future. Importantly, mood disorders have been associated with less positive expectations about the future.

Aims: To investigate the cognitive mechanisms which underlie how future prospects impact our mood in response to current decision outcomes, and how this may be aberrant in people with depression.

Methods: Fluctuations in mood in response to probabilistic outcomes were assessed in healthy participants (N=42) using a gambling paradigm with frequent experience sampling on mood. Participants made decisions between safer and riskier gambles in Gain blocks, where they could win points, and Loss blocks where they could lose points. Importantly, participants were shown whether the next two blocks of trials were Gain or Loss blocks to assess the effects the future prospects on both mood and behaviour.

Results: We adapted an established computational model that explains mood fluctuations based on recent rewards and prediction errors (Rutledge, et al., 2014) to include parameters which modulated mood based on future prospects. Bayesian model comparison suggests that future Gain blocks increase mood, while future Loss blocks decrease mood. However considerable individual differences in how future prospects modulate mood were also revealed.

Conclusion: Future prospects impact upon mood in response to current decision outcomes, however the underlying mechanism for this interaction remains unclear. I will present ideas for future modelling of this task alongside model simulations.

S2-P03

Title: Cognitive Subtypes in First-Episode Psychosis: An Empirical Longitudinal Study of Relationship to Cognitive, Symptom and Functional Outcomes.

Watson AJ[1], Deakin B[2], Suckling J[3], Dazzan P[4], Lawrie SM[5], Upthegrove R[6], Husain N[2], Chaudhry I[2], Dunn G[1], Jones PB[2], Lisiecka D[2], Lewis S[1], Barnes TRE[7], Williams S[3], Hopkins S[2], Knox E[2], Byrne K[2], Drake R[2], Smallman R[2], Joyce E[1]
[1]University College London, [2]University of Manchester [3]University of Cambridge, [4]King's College London, [5]University of Edinburgh, [6]University of Birmingham, [7]Imperial College London

Background: Variable outcomes following a first-episode of psychosis are partly attributable to heterogeneity in cognitive functioning. Previous work in first episode psychosis has identified clinically meaningful cognitive subtypes based on pre-specified differences in estimated premorbid and current cognitive functioning. **Aims**: To use an empirical clustering technique to examine whether these cognitive profiles can be replicated with an unbiased method, their relationship with clinical, cognitive and global functioning as well as their stability over time.

Methods: Patients were recruited following a first episode of psychosis. Participants were assessed on clinical, cognitive and global functioning at baseline (n=169) and 12-month follow-up (n=107). K-means analysis was used to cluster participants on the basis of premorbid IQ (WTAR), and baseline cognition. Clinical and global functioning was assessed using the Positive and Negative Syndrome Scale (PANSS) and Global Assessment of Functioning (GAF).

Results: K-means cluster analysis revealed three cognitive subgroups: 28% showing preserved premorbid and current IQ (PIQ); 29% displaying compromised premorbid and current IQ (CIQ); and 43% with normal premorbid but deteriorated current IQ (DIQ).There were significant differences between groups on all cognitive measures at baseline. At 12-months, the PIQ and DIQ groups significantly improved on negative and general symptom scales. At follow-up there were significant differences between groups in negative syndrome scores.

Conclusion: Using an empirical method to define cognitive subgroups, we replicated previous findings that a subgroup of patients show decline in IQ by psychosis onset. Twelve-months later this subgroup had neither continued to deteriorate nor returned to pre-morbid levels of cognition.

S2-P04

Title: Probability judgements in decision-making contexts involving deception

Fries A[1], Pilditch T[2], Lagnado D[2]

[1]UCL Institute of Neurology, [2]Division of Psychology and Language Sciences, UCL

Background: Bayesian frameworks of probabilistic and evidential decision-making have sparsely been applied to contexts involving deceptive information. Although previous research has focused on how deception can be measured or detected, it has not focused on how to effectively model the influence of a potentially deceptive source on evidence integration and belief updating.

Aims: This study aimed to characterise agents' reasoning and judgment under uncertainty when provided with potentially deceptive sources of information in predefined decision-making contexts. To compare a normative against a descriptive model of reasoning and judgment, we investigated to what extent participants' inferences correspond to a Bayesian probability framework upon the introduction of potentially deceptive information.

Methods: Participants from across the UK were recruited and reimbursed in an online study. In legal decision-making context, participants needed to make several probabilistic judgements about sequentially provided pieces of statistical evidence. This information included potentially deceptive information. Normative Bayesian models of belief updating were compared to descriptive data to investigate their differences.

Prospective results: Although we lack results at this stage, we predict that people's belief updating will deviate from normative Bayesian models in two important ways. First, participants are expected to underestimate the evidence provided by potentially deceptive sources of information in the condition in which they are non-deceptive. Second, we expect an exponentially growing weight of the information provided by independent but relatively unreliable sources of information on belief updating.

S2-P05

Title: The Cognitive Profile of Superficial Siderosis

Flores Martin A[1], Banerjee G[1], Chan E[2], Werring D[1]

[1]Stroke Research Centre, UCL Institute of Neurology, [2]Department of Neuropsychology, National Hospital for Neurology and Neurosurgery

Background: Superficial siderosis (SS) is a radiological finding identified on blood sensitive sequences (e.g. SWI, T2*-GRE). It describes linear deposition of haemosiderin within the layers of cortex and spinal cord. This can be infratentorial (iSS) or cortical (cSS). iSS is associated with the clinical syndrome called "classical siderosis" of the CNS, which presents with ataxia, hearing impairment, and myelopathy and may have supratentorial involvement. cSS only involves supratentorial structures and is associated with cerebral amyloid angiopathy (CAA). cSS is present in greater numbers in memory clinics and its presence predicts progression to dementia. This project intends to answer whether SS is toxic or a marker of severe CAA.

Aims: To investigate whether there are individual neuropsychological domains that are susceptible to SS and compare iSS with CAA SS.

Methods: We will include patients attending a specialist neurovascular clinic with either iSS (n=12) or probable CAA (according to the modified Boston criteria) who have neuropsychological data. We will compare the neurocognitive profiles of individuals with iSS and CAA with c-SS. We will analyze data by univariable comparisons.

Results: We hypothesize that SS is toxic and predict that the iSS patients will have decreased neuropsychological performance. A difference between c-SS and iSS will be described and susceptible neuropsychological domains identified.

Conclusion: SS is toxic to the brain and deterioration in neurocognitive profiles of patients is not just due to CAA.

S2-P06

Title: Self-development during adolescence: Is mentalising associated with self-knowledge?

Scheuplein M[1], Ahmed S[1], Foulkes L[2], Griffin C[1], & Blakemore S-J[1]

[1]*UCL Institute of Cognitive Neuroscience,*[2]*Department of Education, University of York, UK*

Background: Mentalising is the ability to infer someone else's mental states, beliefs, and intentions. Self-referential processing is the ability to draw on self-knowledge. Both abilities are known to undergo continued development during adolescence. Research in adults suggests an interplay and mutual dependence between self-referential processing and mentalising about others. However, little is known about the relationship between these two abilities in adolescence.

Aims: To investigate age differences in self-referential processing and mentalising between adolescence and adulthood. Also, by looking at the association between mentalising and self-referential processing.

Methods: Participants were adolescents (N = 30, aged 11-17) and adults (N = 30, aged 23-35), recruited from the Greater London area. The self-reference effect was assessed by testing memory performance for self-related adjectives vs. non-self-related adjectives (adjectives describing a town). Mentalising ability was assessed using the Director task (Dumontheil, Apperly, & Blakemore, 2010). The WASI Matrix Reasoning test was also administered as a measure of IQ.

Results: Preliminary data analysis suggests that adults were better at the mentalising task and remembered more non-self-related adjectives than adolescents. In contrast, adolescents showed poorer performance on the mentalising task and better memory for self-related adjectives compared with adults.

Conclusion: This study provides evidence that mentalising abilities continue to develop across adolescence. Furthermore, self-referential processing appears higher in adolescents relative to adults.

S2-P07

Title: Cognitive Mechanisms of Contextual Fear Conditioning

Settle R[1], Bush D[1], Bisby J[1], Castegnaro A[1], Burgess N[1]

[1]*UCL Institute of Cognitive Neuroscience*

Background: Learning and remembering the location of aversive or fearful stimuli – a process known as contextual fear conditioning - is critical for the survival of all animals.

Aims: To elucidate the cognitive mechanisms that supporting contextual fear conditioning in humans.

Methods: On a desktop PC, participants explored two visually distinct virtual reality (VR) environments that each contained two beehives – one on either side of the environment. Participants were tasked with 'picking' visible flowers distributed across each environment. Unknown to the participant, one environment was 'dangerous', such that participants would receive an electric shock with 60% probability whenever they picked a flower in one half of that environment. After picking a flower, participants were frozen and asked to rate their expectancy of shock from 1 to 10. To increase the duration of learning, the dangerous half of the dangerous environment was changed half way through the experiment. In addition, skin conductance responses (SCR) were recorded throughout.

Results: We are currently analysing changes in shock expectancy ratings and SCR during the period that participants were frozen prior to potential shock.

Predictions: We predict that expectancy ratings and SCR will come to predict the aversive contingencies of the dangerous half of the dangerous environment, and that the time taken to pick flowers in that area will be longer, indicating aversive behaviour as a result of fear conditioning.

S2-P08

Title: Behavioural evidence for pattern separation in human episodic memory

Zotow E[1], Bisby JA[1,2], Burgess N[1,2]

[1]UCL Institute of Cognitive Neuroscience, [2]UCL Institute of Neurology

Background: Personally experienced events are thought to be stored in episodic memory as coherent representations, and an essential feature of this system is the ability to discriminate similar experiences. Hippocampal pattern separation is proposed to play a fundamental role in this process, storing discrete orthogonalized representations and thus reducing interference from similar competing memories.

Aims: To examine whether overlapping memory representations are stored independently from each other, consistent with the idea of pattern separation.

Methods: Participants encoded multi-element events comprising a person, location and object. Some events were paired in that they shared a common element (e.g., the same person). Memory was then tested across all event associations and in each direction (e.g., person-location, location-person). We used a measure of dependency to test whether the probability of successfully retrieving one association within an event is dependent on retrieval of all other associations from the same event. We also examined the amount of dependency in retrievals from across overlapping and non-overlapping events.

Results: Dependency was seen within each event, consistent with the idea that events are stored as coherent representations. We also found that non-overlapping events were stored independently from each other. Interestingly, we saw that for overlapping pairs, performance on one event was negatively correlated with performance on its matched event.

Conclusions: Our findings show that overlapping memories are 'negatively dependent'. This may reflect the separation of patterns of corresponding memory representations at the neural level.

S2-P09

Title: The relationship between visual speech, phonological awareness and reading in hearing children.

Worster E[1], Pimperton H[1], Hulme C[2], MacSweeney M[1,3]

[1]UCL Institute of Cognitive Neuroscience, [2]Department of Education, Oxford University, [3]Deafness, Cognition and Language Research Centre, UCL

Background: Although hearing people predominantly rely on auditory speech during speech perception, visual information is also important. Speechreading (lipreading) skill strongly correlates with current reading ability in deaf children (Arnold & Kopsel, 1996; Kyle, Harris & MacSweeney, 2016; Harris et al., 2017) and also in hearing children (Kyle & Harris, 2011; Kyle et al, 2016). We previously found that in deaf children this relationship between speechreading and reading is fully mediated by phonological awareness.

Aims: To test this model with hearing children. We predicted that the relationship between speechreading and reading would be mediated by phonological awareness.

Methods: 138 5-7 year old hearing children watched silent videos of people speaking and identified what the person was saying. They also completed the following subtests from the York Assessment of Reading Comprehension: early word reading; single word reading; sound deletion.

Results: We showed that, as predicted, there was a strong correlation between the speechreading and reading variables (ß = 0.610) and that this relationship was fully mediated by phonological awareness (ß = 0.079 after mediation).

Conclusion: Even when children have full access to auditory speech information, visual speech information contributes to phonics representations and the relationship between speechreading and reading is fully mediated by phonological awareness. The findings suggest that teachers should emphasize visual as well as auditory information during phonics instruction.

S2-P10

Title: The processing of laughter in people with autism

Cai QC[1], Chen SHY[1], White S[1], Scott S[1]

[1]UCL Institute of Cognitive Neuroscience

Background: Laughter is a universal non-verbal emotional vocalisation in human beings. As a social vocal emotion, the engagement of mentalising ability is crucial in the processing of laughter's social functions and using it as a social signal in daily interaction, resulting in a long-term benefit in people's social life well-being.

Aims: To investigate laughter processing in people with autism would extend our knowledge of the role laughter plays in establishing and maintaining social bonds. Moreover, it is essential for the characterisation of the relationship between cognitive and affective mentalising and social interactions in autism.

Methods: Behavioural studies are proposed to investigate the implicit and explicit processing of laughter in people with autism and matched groups of neuro-typical controls. Future research will investigate the role the mentalising system and orofacial mirror system plays in the processing of laughter in people with autism using neuroimaging techniques (e.g. fMRI).

Results: In the process of collecting data. However, in my previous MSc project, we found that relative to TD adults, ASD adults performed less well in distinguishing the spontaneous and social laughter. In addition, the perceived contagion of laughter by ASD adults is less influenced by the type of laughter.

Conclusion: We predicate that autistic individuals have difficulties in processing spontaneous and social laughter relative to neuro-typical people, suggesting that a high level of cognitive skill such as mentalising ability is crucial in social emotion perception.

S2-P11

Title: Social cognition outcomes following Traumatic Brain Injury

Chan H Y V[1]

[1]*UCL Institute of Neurology*

Background: Recent research and clinical observations showed considerable number of patients with average of higher score on neuropsychological batteries suffered from social cognition deficits following traumatic brain injury (TBI), suggesting dissociations between executive functioning and social cognition.

Aims: The purpose of this study is to investigate the social cognition deficits in TBI patients who had normal executive functions, and the relationships between different aspects of social cognition.

Methods: 25 TBI patients will be recruited to participate in the study. Patients will undergo standard neuropsychological batteries and several social cognition tests. Control social cognition test scores will be taken from normative database as a baseline reference to analyse social cognition deficits in TBI patients.

Results: We hypothesise that (1)TBI patients performed worse in social cognition tests than normal population, (2)Deficits in emotion recognition positively correlate with deficits in ToM, and (3)Deficits in ToM positively correlate with deficits in social judgement and awareness.

Conclusion: The results of this study may contribute to better understanding in the social difficulties faced by TBI patients, hence shedding light on possible support, intervention and rehabilitation for this clinical population. This study will contribute to the development of clinical evaluation tool for social difficulties in TBI patients.

S2-P12

Title: The effects of Cannabidiol on reward processing. A systematic review.

Yim LL[1], Freeman T[2], Bloomfield MAP[3],

[1]UCL Institute of Cognitive Neuroscience, [2]Institute of Psychiatry, Psychology & Neuroscience, King's College London, [3]Division of Psychiatry, UCL

Background: Cannabidiol (CBD) is being investigated as a potential treatment for reward dysfunction disorders, including addictions, depression and psychosis. CBD's therapeutic effects in these psychiatric disorders are potentially mediated by its effects on reward processing.

Aim: To summarize the results of both animal and human studies on the effects of CBD on monetary reward learning, anticipation and consumption.

Methods: Electronic searches on PUBMED and examination of reference lists of relevant articles were performed. Included studies that evaluated the outcomes of CBD administration on at least one of the following: motivation, willingness or behavioural response to earn a reward; subjective, neural or physiological response to reward anticipation and/or reward delivery/feedback; or indices of reward learning. Rewarding stimuli (rewards) were defined as any kind of primary rewards and secondary rewards.

Results: 16 studies (5 human studies and 11 animal studies) were included. CBD consistently reduced the likelihood of relapse, recurrent drug-seeking behaviours and the magnitude of the rewarding feelings induced by addictive substances, as well as drug-conditioned rewards in a dose-dependent manner, only when CBD is administrated in the reinstatement or re-exposure stage. CBD did not affect the subjective rating of a reward in humans. CBD did not differ from placebo in any subjective and behavioural measures in the reinforcement phase.

Conclusion: CBD attenuates reward anticipation, and motivations for reward-seeking in established rewards. It restored the over-sensitised reward processing induced by addictive substances without interfering consummatory rewards. Secondly, CBD plays little or no role in reward learning.

S2-P13

Title: The effects of cannabidiol on emotional processing and anxiety: a systematic review

Yamamori Y[1,2], Freeman TP[3], Bloomfield MAP[2]

[1]UCL Institute of Cognitive Neuroscience, [2]UCL Division of Psychiatry, [3]KCL National Addiction Centre, Institute of Psychiatry, Psychology and Neuroscience

Aims: To systematically review the literature on the effects of CBD on emotional processing and anxiety.

Methods: We performed a systematic literature search across the PubMed database across all articles using the search terms 'cannabidiol' and 'emotion' or 'anxiety' or 'mood' or 'face'. Experiments and studies comparing similar conditions except for the relative presence of CBD in humans were included.

Results: A total of 24 articles were included. Nine out of 21 studies that tested for the subjective effects of CBD on anxiety found significant subjective effects. Three studies tested for the cognitive-affecitve effects on CBD, and significant effects were found in the domains of attention, memory and perception of emotional information. Neurocognitive effects of CBD were investigated by five studies, which converge on the hypothesis that CBD produces inhibitory effects on the limbic circuit.

Conclusions: The evidence for CBD's anxiolytic effects is not consistent, yet there are robust effects that are evident from the literature. CBD appears to be most powerful for individuals in a heightened state of anxiety. Significant effects were observed in multiple domains of cognitive processing relevant to emotion. Finally, CBD elicits effects on limbic activity which is critical for emotional processing.

S2-P14

Title: 'Tablet-based auditory comprehension therapy after stroke: are items learnt as part of a phrase or as a single lexical unit?'

Leff AP[1], Fleming V[1], Valton V[1], **Upton E[1]**

[1]*UCL Institute of Cognitive Neuroscience*

Background: Suffering from a stroke can result in complex language disorders known as aphasia and around 48% of aphasic people experience auditory comprehension impairments (Breese &Hillis, 2004,). Currently, however, there is limited evidence that supports the effectiveness of treatment for this deficit. Research that assesses the variables associated with positive therapeutic outcomes is required to maximise the efficacy of intervention and improve patient outcomes.

Aims: To examine whether aphasic patients' auditory comprehension of single words improved due to the learning of single lexical units, or the learning of specific phrases, on a set of trained items in a tablet-based word/sentence-to-picture matching therapy programme ('Listen-In').

Methods: A randomised cross over trial was used in which a 12-week block of therapy was compared to a 12-week block of standard care. A novel auditory comprehension assessment was completed at baseline, pre-intervention and post-intervention. These results were combined with Listen-In therapy data and a hierarchical multi-level logistic-regression was used to model success/failure of trial-by-trial behaviour for each participant.

Results: Preliminary findings indicate that the learning of items within a specific phrase better accounted for improved auditory comprehension. Full data analysis will be available for the poster.

Conclusion: Results from this study will demonstrate how item-based therapy algorithms can be optimised for individual subjects (precision rehabilitation) with language comprehension impairments.

S2-P15

Title: Assessing the Preparedness of Patients with Functional Neurological Symptoms after undergoing Preparatory Therapy using Psychometric Evaluation Scales

Papadopoulos E[1], Moutoussis M[1,3], Selai C[1,2,3]

[1]UCL Institute of Neurology, [2]UCL Department of Motor Neuroscience and Movement Disorders, [3]National Hospital for Neurology and Neurosurgery

Background: Functional Neurological Symptoms (FNS) is a debilitating heterogeneous condition with no organic basis yet known to explain its emergence.

Aims: To investigate whether a Preparatory Therapy given before FNS patients enter an inpatient multidisciplinary team (MDT) programme improves the "preparedness" of patients, leading to improved therapeutic output.

Methods: An online Preparatory Therapy was prepared to inform patients about FNS, how to identify unreasonable thoughts which exacerbate symptoms, how to deal with these thoughts, and helpful goal strategies that allows the patients to improve their symptoms. A psychometric clinician-rated outcome measure (CROM) and patient-reported outcome measure (PROM) scale was made to evaluate the "preparedness" of a patient after having undergone the Preparatory Therapy. The CROM is finished, the PROM is in its pilot phase.

Results: The mean CROM score on a scale from 15-75 of increasing preparedness based on 3 patients is 52.16.

Conclusion: The project is currently in its data collection phase, there can be no conclusive statements made yet. What the researchers expect to see is that on average, patients and clinicians will rate the patient as having significantly improved preparedness from the Preparatory Therapy. What the researchers are looking forward to seeing is what the internal consistency of the CROM and PROM will be, as well as how strong the interrater agreement is.

S2-P16

Title: Tractography-informed resting-state fMRI segmentation of the thalamus for improved deep brain stimulation targeting in essential tremor

Bergman J[1], Zrinzo L[1,2], Akram H[1,2]

[1]Unit of Functional Neurosurgery, UCL Institute of Neurology, [2]Victor Horsley Department of Neurosurgery, National Hospital for Neurology and Neurosurgery

Background: Deep brain stimulation (DBS) of the ventral intermediate nucleus (VIM) of the thalamus is a well-established surgical intervention for medication-refractory essential tremor (ET). Template atlas coordinates inform the placement of electrode(s) in the VIM target during awake neurosurgery. Electrode placement accuracy is verified by intraoperative test stimulation, as traditional MRI sequences are unable to resolve thalamic subnuclei boundaries. Probabilistic tractography using resting-state functional MRI (rfMRI) can resolve thalamic subnuclei, allowing precise VIM targeting during asleep neurosurgery – improving patient comfort, electrode placement accuracy and post-operative outcomes.

Aim: To triangulate the location of the VIM using rfMRI functional connectivity of the primary motor area (M1) and the dentate nucleus of the cerebellum to the thalamus.

Materials and Methods: Open-source MP-RAGE and rfMRI data gathered from twelve healthy subjects with 3T Siemens MRI (voxel size 3mm3) were preprocessed, denoised and analysed in CONN toolbox (MATLAB). First-level seed-based correlation (weighted general linear model) and second-level seed-to-voxel analysis were performed to identify functional connectivity between M1 and cerebellar dentate seed regions and thalamic voxels.

Results: The dentate-rubro-thalamo (DRT) tract was visualised using graph theory models of M1, thalamic and dentate connectivity. Seed-to-voxel functional connectivity maps with M1and dentate seed regions reveal thalamic voxel activation at rest. We expect further seed-to-voxel connectivity analyses to yield quantifiable thalamic voxel activation corresponding to the VIM.

Conclusion: Functional connectivity mapping using rfMRI may allow for patient-specific VIM localisation, eschewing the need for template atlas guidance and awake ET DBS surgery, likely improving patient-comfort and post-operative outcomes.

S2-P17

Title: A cross-sectional exploratory magnetic resonance imaging study evaluating white matter diffusion measures for the overactive bladder in Multiple Sclerosis

Yang X[1,2], Liechti1 MD[1], Prados Carrasco F[2], Yiannakas MC[2], Gonzales G[3], Toosy AT[2], Gandini Wheeler-Kingshott CAM[2], Panicker JN[1,3]

[1]UCL Institute of Neurology, Department of Brain Repair & Rehabilitation and Department of Uro-Neurology, The National Hospital for Neurology and Neurosurgery, [2]Queen Square MS Centre, Department of Neuroinflammation, UCL Institute of Neurology, [3]Uro-Neurology Department, The National Hospital for Neurology and Neurosurgery, London, United Kingdom

Background: Lower urinary tract symptoms (LUTS) is described in more than 80% of the multiple sclerosis patients and has a pronounced impact on patients' quality of life. The most common LUTS are the overactive bladder (OAB) symptoms. However, the white matter (WM) changes regarding the OAB symptoms in MS are poorly understood.

Objectives: To determine the structural WM changes between MS groups (MS without LUTS vs MS with OAB), and the associations between diffusion measures and clinical scores of OAB in MS.

Methods: Magnetic resonance imaging (MRI) were carried out to get diffusion measures and lesion volumes in WM, on twenty-six right-handed female MS patients (mean age = 46.1 years). The Urinary Symptom Profile (USP) questionnaire was used to test the severity of the OAB symptoms.

Results: There is a lower fractional anisotropy (FA) spread in WM in frontal lobes and the non-dominant hemisphere in MS with OAB group, compared with MS without LUTS group ($p < 0.08$). As the OAB sub-score in USP questionnaire increases, the FA decreases in both side WM in frontal lobes and parietal lobes ($P < 0.05$).

Conclusion: It is considered the OAB symptoms is related to the WM changes in MS.

S2-P18

Title: Monitoring single-synapse presynaptic calcium dynamics in a mouse model of migraine

Tyurikova O[1,2], Nicholson E[1], Kullmann DM[1], Rusakov D[1], Volynski KE[1]
[1]1UCL Institute of Neurology, [2]N. I. Lobachevsky State University of Nizhny Novgorod, Russia

Background: Familial Hemiplegic Migraine type 1 (FHM1) is a rare inherited form of a migraine caused by mutations in the CACNA1A gene, encoding the α1 pore-subunit of voltage-gated Ca2+ channel CaV2.1. These channels are the major trigger of action potential (AP)-evoked neurotransmitter release in central synapses.

Aims: Investigate the effects of S218L FHM1 mutation on presynaptic Ca2+ dynamics and synaptic transmission.

Methods: Acute whole brain coronal slices (300 μm) where prepared from young (p18-p27) and aged (5-9 month old) S218L knock-in mice. Whole cell patch-clamp recordings were performed from pyramidal neurons of layer 2/3 visual cortex with the KMeSO3-based intracellular solution, supplemented with the morphological tracer Alexa-594 (50 μM) and the Ca2+ fluorescence indicator Oregon Green BAPTA-1 (300 μM).

Results: Nanomolar sensitive FLIM recordings from individual presynaptic boutons show that S218L mutation doesn't affect basal [Ca2+] but leads to the reduction of AP-evoked Ca2+ influx in young mutant mice. In contrast, aged mutant mice show elevated baseline [Ca2+] and increased AP-evoked Ca2+ influx. Changes in evoked Ca2+ dynamics correlated with the differential regulation of the AP waveform at different age. **Conclusion**: S218L FHM1 mutation leads to a loss of CaV2.1 function in young mice and gain of function in aged mice, illustrating an age-dependent homeostatic mechanism in the pathophysiology of a migraine.

S2-P19

Title: Differentiating tumour progression from benign treatment effects of stereotactic radiosurgery in patients with cerebral metastases

Patel M[1], Ferst N[2], Kitchen N[3], Thust S[1], Hyare H[1]

[1]UCL Institute of Neurology, [2]Department of Oncology, UCLH, [3]Department of Neurosurgery, NHNN

Background:Stereotactic radiosurgery (SRS) is first-line treatment for patients with brain metastases, usually to aid palliation though long-term survival has been seen in subgroups of patients. In the post-treatment MRI scan hyperintensity is usually seen, rendering it difficult to differentiate benign effects of treatment from true progression of tumour.

Aims:To assess which conventional MRI features can predict treatment response, and the value of T1 subtraction maps and pCASL perfusion-weighted imaging (PWI).

Methods: Retrospective analysis of pre-/post-treatment structural MRI scans of patients treated with SRS for brain metastases at UCLH: changes in tumour volume will be quantified using ITK-snap, textural changes assessed using in-house software, T1 subtraction maps calculated and PWI maps analysed using FSL (figure). Qualitative and quantitative MRI features will be correlated with treatment dose and overall survival (OS).

Results/reflection: 58 patients were identified (37 females, 21 males) who underwent SRS at UCLH between Jan-15 and Dec-16 for brain metastases from a range of known primaries (lung 37.9%, breast 27.6%, melanoma 24.1%, other 10.4%). We expect presence of necrosis or intralesional haemorrhage to predict benign treatment response and improved OS. We expect T1 subtraction maps to demonstrate improved detection of new metastases and hyperperfusion to predict tumour progression.

Conclusion: Our expectation is increased volume, along with specific textural changes like haemorrhage/necrosis correlate to benign treatment effects and improved OS whilst hyperperfusion predicts tumour progression and poorer OS.

S2-P20

Title: Abnormal hippocampal structure and function in patients with Juvenile Myoclonic Epilepsy and unaffected siblings: a magnetic resonance imaging study

Caciagli L[1,2], Wandschneider B[1,2], Xiao F[1,2,3], Vollmar C[1,2,4], Centeno M[1,2], Trimmel K[1,2], Vos SB[1,2,5,6], Lowe A[1], Thompson PJ[1,2], Winston GP[1,2], Duncan JS[1,2], Koepp MJ[1,2]
[1]Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, [2]MRI Unit, Epilepsy Society, [3]Department of Neurology, West China hospital of Sichuan University, [4]Department of Neurology, Ludwig-Maximilians-Universität, [5]Wellcome/EPSRC Centre for Interventional and Surgical Sciences, UCL, [6]Translational Imaging Group, UCL

Background: Juvenile myoclonic epilepsy (JME) is a generalised epilepsy syndrome with complex polygenetic aetiology. Imaging studies detected fronto-cortical abnormalities and impaired fronto-cortico-subcortical connectivity in patients with JME and their unaffected siblings. The presence of hippocampal abnormalities and associated memory deficits is controversial, and fMRI studies in JME have not tested hippocampal activations.

Aims: To investigate episodic memory and highlight the imaging correlates of hippocampal structure and function in patients with JME and their siblings.

Methods: *37* JME patients, 16 unaffected siblings and 20 healthy controls were studied with automated hippocampal volumetry, qualitative and quantitative morphometric assessments to detect hippocampal malrotation, neuropsychometry and an event-related verbal and visual memory fMRI paradigm addressing mesiotemporal function.

Results: A reduction of left hippocampal volume (5-8%) was detected in patients and their siblings compared with controls ($p<0.01$). Unilateral or bilateral hippocampal malrotation was identified in 51.4% of patients and in 50% of siblings, against 15% of controls ($p<0.05$). Quantitative measures suggesting abnormal hippocampal verticalisation were found both in patients and siblings ($p<0.05$). No overt impairment of verbal and visual memory was identified with neuropsychometry. Functional mapping highlighted atypical patterns of hippocampal activation in JME and siblings ($p<0.05$, corrected).

Conclusion: In patients with JME and their siblings, hippocampal morphometric abnormalities span from volume loss to atypical hippocampal shape and positioning, relate to reorganisation of function, and are likely the expression of an underlying neurodevelopmental mechanism. Co-segregation of hippocampal morphometric markers in patients and unaffected relatives is suggestive of a genetic imaging phenotype, independent of disease activity.

S2-P21

Title: Simultaneous intracranial EEG-fMRI in a word-generation task

Talami F[1,2], Trébuchon A[3,4]., Dubarry A.-S[4,5]., Chaudary U., Lemieux L[1,2].

[1]Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology,[2]MRI Unit, Epilepsy Society Chalfont St Peter, [3]Aix-Marseille Université, CNRS, LPC,[4]Aix-Marseille Université, APHM, Hôpital de la Timone, Service de Neurophysiologie Clinique, [5]Aix-Marseille Université, INSERM, INS, Marseille, France

Background: Simultaneous EEG-fMRI recordings provide a wide range of complementary information. Compared with scalp EEG, intracranial EEG can capture more subtle and local features of electrophysiological activity and may therefore offer novel insights into the relationship of such features with concurrent BOLD signal changes.

Aims: To investigate the relationship between BOLD signal and the gamma band oscillations related to a word-generation task and improve our understanding of the human brain network involved in language production in patients with focal epilepsy.

Methods: Seven patients with epilepsy having electrodes placed over their peri-sylvian cortex, as part of their presurgical evaluation, underwent a simultaneous icEEG-fMRI session of a silent phonological verbal fluency task. A block design was used, with 30s of task followed by 30s of rest.

Results: Intracranial EEG studies in humans have shown that several perceptual, motor and cognitive processes are related to focal power increases in the gamma band. A close correspondence may indeed exist between gamma band oscillations and local haemodynamic signals variation revealed by fMRI. Testing this prediction implies identifying EEG sites with a task-dependent difference in gamma power and estimating the relationship between such sites and the activation network revealed by fMRI.

Conclusion: Linking fMRI and icEEG in complex cognitive task would allow to combine them into fine brain mapping procedures with high temporal and spatial resolution.

S2-P22

Title: Systematic Review and Meta-analysis: Arterial Spin Labelling (ASL) Efficiency in Adults Glioma Grading

Amirah Alsaedi[1], Fabio M. Doniselli[2], H.R. Jäger [1], Xavier Golay[1], Sotirios Bisdas[1]
[1]Department of Brain Repair & Rehabilitation, UCL Institute of Neurology, [2]Postgraduate School in Radiodiagnostics, University of Milano

Background: ASL has been reported as an effective method in distinguishing between high-grade-gliomas-(HGG) and low-grade-gliomas-(LGG). However, some studies reported that ASL is unable to stratify glioma grades.

Aim: To overcome these discrepancies in results of the applied ASL in adult gliomas.

Methods: We conducted a systematic review to evaluate the efficacy of arterial spin labelling-(ASL) in staging of gliomas. For this purpose, EMBASE & MEDLINE were consulted. QUADAS-2 was used for quality appraisal. Resulted in selection of 18 studies: 8 of the included studies declared tumour blood flow-(TBF) and relative-TBF-(rTBF) values as a mean and SD; 3 stated cut-off values and sensitivity/specificity levels; while the remainder addressed both. Statistical analyses included random-effects-model, forest-plots, system for modelling specificity and sensitivity outcomes, and hierarchical summary ROC curve.

Results: The absolute tumour blood flow-(TBF) value could distinguish between HGG and LGG. It could not distinguish between WHO grade-2/3 or between grade-3/4. rTBF was more effective in glioma grading (between grade-2/3 and between grade-3/4, p-value <0.001 and 0.008, respectively). Moreover, in the sensitivity and specificity analyses, rTBFmax showed the highest levels of accuracy for glioma grading.

Conclusion: ASL mostly in terms of rTBF, especially rTBFmax, is useful for baseline glioma grading.

S2-P23

Title:Towards Connectomic Functional Neurosurgery

Akram H[1], Foltynie T[1], Limousin P[1], Jahanshahi M[1], Mahlknecht P[1], Georgiev D[1], Hyam J[1], Devita E[1], Hariz M[1], Ashburner J[1], Behrens T[1], Zrinzo L[1]
[1]*The Unit of Functional Neurosurgery, Sobell Department of Motor Neuroscience and Movement Disorders, UCL Institute of Neurology*

Background: Success of functional neurosurgical procedures hinges on proper patient and target selection, and on accurate lead placement. Advancements in imaging techniques in the last century provided a window into the brain, however; targeting deep brain structures continued to pose challenges due to the difficulty in localizing the functionally distinct sub-regions within the basal ganglia and thalamic targets using conventional magnetic resonance imaging.

Aims: To utilise MRI connectivity to visualize targets not readily visible on MRI and provide new ways to define the sub-regions in target nuclei, thus optimising targeting to improve efficacy and avoid unwanted side effect. Connectivity studies also provide a tool for examining the underlying pathophysiology and mechanism of action of deep brain stimulation (DBS). Moreover, the exploration of predictive biomarkers can further help in patient selection.

Methods: Forty-two patients underwent advanced diffusion MRI and resting-state fMRI prior to DBS surgery for Parkinson's disease, tremor**,** cluster headache and obsessive compulsive disorder (OCD). Structural and functional connectivity were correlated with clinical outcomes one-year after surgery.

Results and conclusion: We present several new analysis methodologies and applications of advanced connectivity imaging to: **(1)** build predictive models of DBS surgery outcome; **(2)** refine the surgical target and **(3)** help build a better understanding of the pathogenesis of the treated conditions and the mechanism of action of DBS therapy.

S2-P24

Title: Improving separation of the amygdala and the hippocampus on MRI from an automated parcellation (GIF): application on a FTD cohort

Wu L[1], Rohrer J D[1], Bocchetta M[1]

[1]*Dementia Research Centre, UCL Institute of Neurology*

Background: GIF is a locally developed atlas-based propagation technique (GIF) that automatically parcellates T1-weighted MRIs into different brain regions. This does not accurately delineate the amygdala and the hippocampus, which are typically affected in frontotemporal dementia (FTD).

Aims: Following initial training on manual segmentation for hippocampus and amygdala, we aim to anatomically improve the delineation of these two nuclei by manually editing their GIF segmentations. We then investigated their volumetric differences between FTD patients and controls when using GIF-derived volumes and the edited volumes.

Methods: Manual hippocampal and amygdalar segmentation was performed using ITK-SNAP. We computed the intra-rater intraclass correlation coefficient (ICC) on 10 subjects. Hippocampal and amygdalar volumes for 30 different subjects were corrected for total intracranial volume for both methods, and used to calculate the differences between 15 FTD patients and 15 controls (Mann-Whitney).

Results: Intra-rater ICCs for the manual segmentations were 0.87-0.90 for the amygdala, and 0.97 for the hippocampus. When comparing FTD vs. control groups, we found 20% and 24% volumetric difference in the right and left amygdala, respectively, and 8% and 16% in the right and left hippocampus, respectively. GIF method detected 16% and 21% difference in the right and left amygdala, and 8% and 12% in the right and left hippocampus. Overall, GIF overestimated volumes by 20% compared to manually edited-regions.

Conclusion: Intra-rater reliability ICC for manual segmentation was high for both nuclei. FTD was associated with atrophy in the amygdala and the hippocampus, consistent with previous studies. Ongoing analysis on a final sample of 110 subjects will additionally investigate potential volumetric differences in these two nuclei in different FTD gene carriers.

S3: Session 3 (11:30 – 12:20)

S3-P01

Title: Investigation of the role of LRRK2 in murine macrophage RAW264.7 cells

Nazish I[1], Warner T[1], Hardy J[2], Lewis P[2,3], Pocock J[4], Bandopadhyay R[1]
[1]Reta Lila Weston Institute of neurological Studies and Department of Molecular Neuroscience, UCL Institute of Neurology, [2]Department of Molecular Neuroscience, UCL Institute of Neurology, [3]School of Pharmacy, University of Reading, [4]Department of Neuroinflammation, UCL Institute of Neurology

Background: Pathogenic mutations and polymorphisms in the leucine-rich-repeat-kinase 2 (LRRK2) gene are linked to familial Parkinson's disease (PD), idiopathic PD and to two inflammatory conditions, leprosy and Crohn's disease. In the brain, LRRK2 is expressed strongly in microglia and macrophages indicating its potential role in innate immunity. How LRRK2 dysfunction causes PD remains ambiguous. LRRK2 protein harbours two critical enzymatic activities, the kinase and the GTPase making it a highly druggable target for potential therapies for PD. Herein, we aimed to establish a link between LRRK2 dysfunction and signalling mechanisms in the murine macrophage cell line (RAW264.7) and the pathological processes in PD.

Materials and Methods: Using WT, T1348N-LRRK2 (this mutation prevents GTP binding) and LRRK2-KO RAW264.7 cell lines, we tested LRRK2 phosphorylation dynamics and TNF-alpha release following treatment with lipopolysaccharide (LPS, a proinflammatory mediator) and after treatment with 4-specific LRRK2- kinase inhibitors. Standard immunoblot procedures were used to monitor LRRK2-phosphorylation at 4 specific phospho-sites and secreted TNF-alpha levels were measured using ELISA. Statistically significant differences were analysed using ANOVA and T-test using Graph-PAD prism.

Results: We observed significant upregulation of LRRK2 phosphorylated at Ser935 and Ser955 residues with LPS (100ng/ml) treatment from 2h-24h in RAW264.7 cell line. Kinase inhibition was found to decrease baseline LRRK2 phosphorylation at 4h with LPS treatment reversing the effect. LPS treatment for 24h and 48h upregulated TNF-alpha secretion following LPS stimulation in both WT and the GTPase-deficient mutant RAW264.7 cells with no significant difference in the basal secretion between the cell lines.
Conclusion: LPS most significantly stimulated phosphorylation of LRRK2 in WT cells and GTPase-deficient RAW264.7 at 4h. Specific LRRK2 kinase inhibitors acted to decrease LRRK2 phosphorylation at Ser935 residue which is a readout of LRRK2 kinase activity. Our preliminary data of TNF-alpha release with LPS treatment appeared to be independent of T1348N mutation.

S3-P02

Title: Pathological, neuroradiological and clinical correlates of B-lymphocytes in multiple sclerosis

Patel A[1], Moccia M[1], Cicarelli O[1]

[1]*Queens Square MS centre, UCL Institute of Neurology*

Background: Demyelination in Multiple Sclerosis (MS) has been largely attributed to B-lymphocyte action in the CNS. B cells are present in immune infiltrates, meninges and parenchyma of MS patients. The mechanisms of B cell infiltration, events preceding their activation (such as oligodendrocyte loss, demyelination and astrocyte activation) and their compartmentalisation with respect to brain region and lesion stage, are now being elucidated. Based on animal studies and post mortem tissue evaluation there is evidence that B-lymphocyte activation is not the only pathway to demyelination, and pathological markers differ with respect to early vs late lesions, altering as the disease progresses.

Aims: This post mortem study of 16 patients compares normal appearing grey and white matter against lesions for quantification of B-lymphocytes. This is correlated with the presence of other pathological and neuroradiological markers such as mitochondrial degradation, microglia infiltration and astrocyte presence amongst others. Quantified data will show any statistical correlation between B lymphocytes and other pathological features in the parenchyma and secondly.

Methods: Cassettes were obtained and histology performed on 16 MS post mortem brains at Imperial College London for analysis at the Queens Square MS centre. Lesions and normal appearing white and grey matter will be identified in each patient and control using 3D Slicer software for medical imaging. Histological data will be extracted for each area using a pipeline previously developed at the Queens square MS Centre UCL.

Results: N/A, MSc project ongoing with completion 14th August.

S3-P03

Title: Frontotemporal dementia: in depth characterization of C9orf72 expansion prevalence in FTD subtypes and bioinformatics analysis.

[1]**Costa B**

[1]*Department of Molecular Neuroscience, UCL Institute of Neurology*

Background: Frontotemporal dementia (FTD) is a neurological disorder that displays severe degeneration of the frontal and temporal lobes. Despite the fact that FTD is clinically, pathologically and genetically heterogeneous, *C9orf72* expansions are critically associated with FTD being among the major genetic causes of FTD.

Aims: To further characterize the prevalence of *C9orf72* expansions in the FTD spectrum (bvFTD, SD, PNFA and FTD-MND) and to characterize *in silico* the functional and biological relevance of C9orf72 in FTD-associated risk pathways.

Methods: The current study includes a significantly large FTD patient cohort (n=900) covering the most significant FTD clinical signatures (see above). *C9orf72* expansions will be characterized by performing Repeat-Primed (RP) PCR analysis on the DNA sample of each patient. The PCR products will be analysed on an ABI3730 DNA analyser and the fragment analysis visualized using GeneMapper Software. Gene and PPI networks will be used to characterize *in silico* the functional environment of *C9orf72*.

Results: We will better characterize prevalence and distribution of *C9orf72* expansions in the different FTD subtypes and improve our understanding of the functional interactomes and cellular processes that are impacted in expansion carriers.

Conclusion: we will make a step forward towards a better understanding and characterization of *C9orf72*-driven FTD etiology and pathogenesis, and potentially highlight new potential biomarkers/drug targets within the C9orf72 interactome

S3-P04

Title: Patient-derived stem cell models of familial British dementia.

E. Augustin[1], C. Arber[1], E. Preza[1], A. Foulkes[2], H. Houlden[1], T. Lashley[3], J. Schott[2] and S. Wray[1]

[1]*Department of Molecular Neuroscience, UCL Institute of Neurology,* [2]*Department of neurodegeneration, Dementia Research centre, UCL Institute of Neurology,*[3]*Queens square Brain Bank, UCL Institute of Neurology*

Background: Familial British dementia (FBD) is a rare neurodegenerative disease caused by a single nucleotide mutation in the stop codon of the type II transmembrane gene (ITM2B). This mutation leads to the addition of 11 amino acids onto the C-terminus of the resulting amyloid bri (Abri) protein that accumulates in patients' brains. The mechanisms linking ITM2B mutations to neurodegeneration are not well characterised and it remains unknown whether the loss of function of ITM2B contributes to the disease. In addition to Abri plaques, tau aggregates are also present in the brains of FBD patients, demonstrating pathological commonalities with Alzheimer's disease. This project aimed to generate induced pluripotent stem cells from two FBD patients and differentiate them into cortical neurons. Cortical neurons were analysed for Abri expression and changes to tau expression. Western blotting was used to analyse protein levels of Abri and its solubility, total and phosphorylated tau. PCR was used to detect RNA products of Abri and tau splicing. Our preliminary results suggest that ITM2B protein levels are unchanged by FBD mutations, reinforcing the hypothesis that FBD mutations lead to a toxic gain-of-function. Ongoing work is investigating tau biology. By investigating disease mechanisms in stem cell models of FBD, this model will help us define specific biological patterns attributable to the dysfunction of the Abri protein and the cellular mechanisms underlying disease.

S3-P05

Title: *In vivo* CRISPR-editing to treat dominant negative mutations causing neurological diseases

Zourray C[1], Snowball A[1], Carpenter J[1], Hughes M[2], Ahad RA[2], Kullmann DM[1] , Schorge S[2], Lignani G[1]

[1]*Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology,* [2]*Department of Pharmacology, UCL School of Pharmacy*

Background: Dominant-negative mutations produce faulty proteins that act antagonistically to wild type (WT) gene products, thereby decreasing their function. For this reason, classical gene therapy approaches involving exogenous gene delivery are inappropriate, and directly correcting the mutation in the genome represents the best option. CRISPR technology has developed rapidly and inserting DNA into post-mitotic cells such as neurons is now possible using homology-independent targeted integration (HITI).

Aims: In this project, we aim to use a CRISPR-based approach to develop first-time treatments for two severe diseases caused by dominant negative mutations in KCNA1 (Episodic Ataxia 1) and GABRG2 (Dravet syndrome). We will use HITI to insert a functional WT exon with a stop codon before the faulty exon in both alleles to prevent the production of the mutant protein.

Methods: Design and test sgRNAs efficiency, design plasmid construct for HITI, test sequence insertion *in vitro* (N2A cells, P19 cells and primary neuron culture) using genomic PCR, AAV-PHP.eB production and injection in mice intravenously via tail vein**,** immunofluorescence, genomic PCR and cerebellar slice electrophysiology.

Results: We have successfully developed a plasmid construct for KCNA1 correction and validated it in different cell lines. We are currently packaging this construct into an AAV-PHP.eB viral vector to test it in primary cultures and *in vivo.* In parallel, we have also designed sgRNAs targeting GABRG2 and we are now testing their efficiency.

Conclusion: The CRISPR-Cas9 system is a promising therapeutic approach for dominant negative mutations causing neurological diseases.

S3-P06

Title: Analysis of α-synuclein post-translational modifications in Idiopathic Parkinson's Disease and Multiple System Atrophy

Sonustun B.[1], Holton JL. [1,2], Bandopadhyay R[1,2]

[1]*Department of Molecular neuroscience and Reta Lila Weston Institute of Neurological Sciences, UCL* ,

[2]*Queen Square Brain Bank, UCL Institute of Neurology*

Background: Aggregated and fibrillar α-synuclein is the main component of Lewy bodies (LBs) and Lewy neurites (LNs) which are the defining pathological hallmarks of Parkinson's disease (PD). The pathological filamentous inclusions in MSA also comprise of abnormally aggregated α-synuclein. α-synuclein can exist in several forms from monomers to oligomers and fibrils and can also be post-translationally modified (PTM) including nitration and phosphorylation. However, which of these forms of α-synuclein are pathogenic remains a matter of intense research.

Objective: To establish whether nitration or phosphorylation of α-synuclein is the predominant PTM in disease pathology in PD and MSA and how this correlate with disease progression.

Methods: Using archival post-mortem human tissue from QSBB, we have studied the expression patterns of a-synuclein PTMs in pathology-affected regions of 15 PD, 5 MSA and 5 neurologically normal controls by immunohistochemistry using novel α-synuclein antibodies made available to us by Hilal Lashuel (Ecole Polytechnique, Switzerland).

Results: The antibodies examined recognized LBs and LNs in IPD. Preliminary analysis suggests that Phosphoserine-129 antibody was particularly sensitive for LNs and dot-like structures in IPD. Nitrated (nY39) α-synuclein antibody detected glial cytoplasmic inclusions (GCI), neuronal cytoplasmic inclusions (NCI) and small threads in MSA pathology.

Conclusion: Both nitrated and phosphorylated forms of alpha-synuclein are present in pathological aggregated inclusions in IPD and MSA. Further analyses of immunohistochemical data and biochemical analysis are underway to explore changes in disease progression.

S3-P07

Title: A cell model for the study of the association of *EIF2AK3*/PERK with PSP

Hapuarachchi B[1], Hamilton J[1], Ehteramyan M[1], Willumsen N[1], Warner T[1], de Silva R[1]

[1]*Reta Lila Weston Institute, UCL Institute of Neurology*

Background: The *EIF2AK3* gene encoding the endoplasmic reticulum unfolded protein response (UPR) sensor, PERK, is a risk factor for the tauopathy, progressive supranuclear palsy (PSP). Activated PERK and UPR markers are associated with tau inclusions in PSP and Alzheimer's disease brains. The associated SNP, rs7571971, is in linkage disequilibrium with coding SNPs, rs867529($Ser_{136}Cys$), rs13045($Gln_{166}Arg$) and rs1805165($Ala_{704}Ser$), forming the coding haplotypes of three highly conserved residues; HapA (conserved): S_{136}-R_{166}-S_{704} and HapB (divergent): C_{136}-Q_{166}-A_{704}. A previous study showed that the divergent risk Haplotype *B* (HapB) has increased PERK activity suggesting that this forms the basis of the genetic risk. The polymorphisms could therefore affect either functional domain (or both).

Aims: The aim of this project is to assess the functional importance of these coding haplotypes.

Results: We generated isogenic HEK293 cell lines for tet-inducible expression of PERK coding haplotypes with a C-terminal myc-tag to discern from endogenous PERK. With Western blot analyses, we demonstrated robust, inducible expression of myc-tagged PERK. Interestingly, with subsequent passages, the HapB PERK variants alone undergo C-terminal cleavage as evidenced by loss of the myc-tag which results not only in increased PERK protein but also reduced activated p-PERK.

Conclusion: This suggests that the increased risk of PSP from the divergent HapB is due to the C-terminal cleavage and reduced PERK activation leading to impaired UPR that could contribute to accumulation of pathological tau.

S3-P08

Title: Huntington's disease phenotypes and disrupted corticostriatal connectivity observed in a novel human iPSC-derived *in vitro* co-culture model.

Casey CS[1,2], Qiu Y[1], Bentham MP[1,3], Smith E[1,2], Lignani G[1], Andre R[1,2], Wood-Kaczmar A[1,2], Tabrizi S[1,2]

[1]*UCL Institute of Neurology,* [2]*Huntington's Disease Research Centre, UCL,* [3]*Sobell Department of Motor Neuroscience and Movement Disorders, UCL*

Background: The corticostriatal (CS) pathway, comprising layer V cortical projection neurons (CPN) and medium spiny neurons (MSN), is one of the first brain pathways to succumb to Huntington's disease (HD) pathology. As a result, disrupted CS connectivity is evident and contributes to the motor and cognitive symptoms experienced by HD patients.

Aims: The aim of this work is to investigate the CS pathway using a purely human tissue-derived *in vitro* system.

Methods: This project utilizes two familial iPSC lines; the control line, with 20/20 HTT CAG repeat lengths (20Q), and a juvenile HD line, with 20/73 CAG repeats (73Q). These lines were differentiated in parallel to either MSNs or CPNs, and co-cultured in microfluidic chambers to physically recapitulate the human CS pathway.

Results: High-resolution fluorescence microscopy has revealed the formation of CS synapses within MFC co-cultures, complimented by live cell imaging with calcium binding dye Fluo4, which demonstrates the successful transmission of calcium between neuronal populations within MFCs. CPN cultures show a HD phenotype in their cytoskeletal dynamics, as axon projection efficiency is drastically reduced in 73Q CPNs compared to 20Q. Furthermore, 73Q MSNs exhibit enhanced cell death after BDNF-withdrawal compared to 20Q cultures. Finally, the intrinsic membrane properties of iPSC-derived MSNs also differ with disease state, as 73Q MSNs are hyper-excitable, with an extended latency to fire and extended refractory period.

Conclusion: These results provide a novel insight into the human CS pathway and suggest subtle differences in both the development and function of the CS pathway in HD.

S3-P09

Title: *In vitro* modelling of mitochondrial disease using human induced pluripotent stem cell (hIPSC) derived myotubes harbouring mtDNA mutations

O'Callaghan B[1], Hanna MG[1], Morgan J[2], Houlden H[1], Madej M[1]

[1]MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, London, [2]Dubowitz Neuromuscular Centre, UCL Great Ormond Street Institute of Child Health

Background: Primary patient fibroblasts and immortalised cybrid lines are the main human cell models currently used to investigate mitochondrial dysfunction caused by mtDNA mutations. Unlike the cell types affected in patients however, these cells are proliferative and rely on glycolytic metabolism for energy production. A more relevant *in vitro* model for exploring disease pathomechanisms and the testing of future therapeutics is desired. **Aims**: To investigate the effect that mtDNA mutations causing Myoclonus Epilepsy with Ragged-Red Fibres (MERRF) and Mitochondrial Encephalopathy, Lactic acidosis, and Stroke-like episodes (MELAS) syndromes have on mitochondrial function in disease relevant myogenic cell types.

Methods: Fibroblasts obtained from patient biopsies harbouring the m.8344A>G MERRF and m.3243A>G MELAS mutations were reprogrammed using non-integrating delivery methods. hIPSC lines were differentiated into myotubes using defined factors which recapitulate developmental signalling gradients during myogenesis.

Results: hIPSC lines harbouring the m.3243A>G mutation show impaired myogenicity compared to isogenic hIPSCs with undetectable levels of m.3243A>G. Unlike the hIPSCs from which they are differentiated, myotubes with high m.3243A>G heteroplasmy show reductions in basal mitochondrial membrane potential and mitochondrial mass.

Conclusions: This *in vitro* model will provide new insight into pathomechanisms of mitochondrial disease in skeletal muscle. Intermediate metabolites affected by mitochondrial mutations may show promise as a supplement based therapy for mitochondrial disease patients.

S3-P10

Title: Heterogeneous nuclear ribonucleoprotein R in frontotemporal lobar degeneration.

LM Gittings[1,2], B Benson[1], AM Isaacs[2], T Lashley[1]

[1]The Queen Square Brain Bank for Neurological Disorders, Department of Molecular Neuroscience, UCL Institute of Neurology, [2]Department of Neurodegenerative Disease, UCL Institute of Neurology

Background: Frontotemporal lobar degeneration (FTLD) is a pathological term used for the description of a pathologically heterogeneous group of disorders affecting in the frontal and temporal lobes. Current neuropathological classification of FTLDs recognises major subgroups characterised by specific proteinaceous inclusions: FTLD-TAU, FTLD-TDP and FTLD-FUS. FUS is a member of the heterogeneous nuclear ribonucleoprotein (hnRNP) protein family and shuttles between the nucleus and cytoplasm. Here we identify an additional hnRNP, hnRNP R, in pathological inclusions in FTLD-FUS and investigate its expression pattern in several FTLD subtypes.

Materials and Methods: We studied the expression of hnRNP R in the frontal and temporal cortices from patients with FTLD-TDP (subtypes A (n= 19), B (n= 3), C (n= 7)); FTLD-FUS (n =5); FTLD-TAU (n=3) and normal control brains (n = 5) using Nanostring Technology. Frontal cortex and hippocampus was used for immunohistochemical analysis to determine the presence of hnRNP R in the FTLD cohort.

Results: hnRNP R was not found in pathological inclusions observed in FTLD-TDP or FTLD-Tau. However hnRNP R was found in FTLD-FUS inclusions from both NIFID and aFTLD-U subtypes. HnRNP R positive neuronal cytoplasmic inclusions and neuronal intranuclear inclusions were found throughout the hippocampus and frontal cortex.

Conclusions*:* FUS and hnRNP R have roles in shuttling mRNA from the nucleus to the cytoplasm. We demonstrate the presence of hnRNP R in the pathological inclusions of FTLD-FUS suggesting it may have a role in the disease mechanism or is a consequence of FUS aggregation.

S3-P11

Title: Developing biomarker assays for progranulin and progranulin-related proteins in frontotemporal dementia.

Emily Abel[1], Martha Foiani[1,2], Ione Woollacott[1], Jonathan Rohrer[1]

[1]Department of Neurodegenerative Disease, UCL Institute of Neurology, [2]UK Dementia Research Institute, London, UK

Background: Frontotemporal dementia (FTD) may be caused by mutations in the progranulin gene (*GRN)*. Individuals with *GRN* mutations have reduced progranulin levels in cerebrospinal fluid (CSF) and blood. Progranulin interacts with sortilin and prosaposin, which may be useful biomarkers in FTD. However, it is unclear how levels of these proteins vary, and relate to each other, in different biofluids.

Aims: First, measure progranulin levels in CSF and plasma of healthy controls and individuals with FTD. Second, develop assays for sortilin and prosaposin using CSF and plasma samples from healthy controls. Determine how levels of these three proteins vary and relate to each other in control CSF and plasma, with a plan to investigate sortilin and prosaposin levels in samples from individuals with FTD. **Methods**: Progranulin levels will be measured using a commercially-available ELISA in CSF and plasma. Sortilin and prosaposin assays will be developed and validated using a variety of ELISAs in CSF and plasma. **Results:** Levels of progranulin are predicted to be normal in healthy controls and sporadic FTD, but lower in individuals with *GRN* mutations. Sortilin and prosaposin may be elevated in cases with lower progranulin levels. **Conclusion**: Levels of progranulin, sortilin and prosaposin are likely to vary within different cohorts and may be useful as biomarkers of disease and therapeutic targets in FTD.

S3-P12

Title: The profile of hnRNP K in Alzheimer's Disease

Low YH[1], Asi Y[1], Lashley T[1]

[1]*Queen Square Brain Bank for Neurological Disorders, UCL Institute of Neurology*

Background: Heterogeneous nuclear ribonucleoproteins (hnRNPs) are a family of well-conserved RNA-binding proteins that are highly involved in cellular processes such as transcription, translation, chromatin remodeling and splicing. Due to its large functional diversity and crucial role in regulating gene expression, dysfunctions in hnRNPs have been linked to many diseases. One of the prominent members, hnRNP-K, has been extensively studied in cancer, however our understanding of hnRNP-K in neurodegeneration is still in its infancy and its profile in AD is largely unexplored.

Aims: The aim of this study is to examine the distribution and burden of hnRNP-K in AD and compare it to controls.

Methods: Post-mortem tissues of AD patients (n=10) and controls (n=10) were sectioned. Immunohistochemistry and microscopic analyses were conducted. Cells were counted manually using ImageJ and categorised according to a set counting criteria. Statistical analyses will be conducted using R.

Results: We predict that AD post-mortem tissue would display more ectopic neurons than controls. This may be marked by cytoplasmic redistribution of hnRNP K into its neuronal processes, as well as punctate neurons with a loss of nuclear staining.

Conclusion: It is likely that AD brains would have more neurons abnormally stained for hnRNP K. This may be due to its high co-localization with TDP-43, which has been found to be abnormal in AD. Misregulation of hnRNP K can also lead to abnormal cell cycle events which may cause cell death.

S3-P13

Title: Stability of blood-based biomarkers of Alzheimer's disease over multiple freeze-thaw cycles

Keshavan A[1,2], Helsegrave A[2,3], Zetterberg H[2,3,4,5], Schott JM[1]

[1]Dementia Research Centre, National Hospital for Neurology and Neurosurgery, [2]Leonard Wolfson Biomarkers Laboratory, Department of Molecular Neuroscience, UCL Institute of Neurology, [3]The DRI Fluid Biomarker Laboratory, UK Dementia Research Insitute at UCL, [4]Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Sahlgrenska University Hospital, [5]Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal

Background: Freeze-thaw instability may contribute to pre-analytical variation in blood-based biomarker studies.

Aims: We measured the effects of up to four freeze-thaw cycles on serum neurofilament light chain (NFL) and plasma total tau, amyloid ß 1-40 ($Aß_{40}$) and amyloid ß 1-42 ($Aß_{42}$).

Methods: Individuals who had peripheral venous blood sampling during investigation of suspected neurodegenerative disease were recruited. After standardised pre-processing, 200µL plasma and serum aliquots were stored at -80°C within 60 minutes of sampling. Aliquots from each individual underwent one to four freeze-thaw cycles. Single molecule array (Simoa) immunoassays were used to quantify each biomarker.

Results: There was no significant difference across four freeze-thaw cycles for serum NFL (n=12), plasma total tau (n=11) or plasma $Aß_{42}$ (n=12). For plasma $Aß_{40}$ (n=14) there was a significant mean reduction of 4.8% and 6.2% at the third and fourth cycles respectively.

Conclusion: Up to four freeze-thaw cycles do not influence Simoa blood biomarkers of NFL, tau or $Aβ_{42}$, with at most minor reductions in $Aβ_{40}$.

S3-P14

Title: Investigating the role of the innate immune system in HD

O'Regan G, Andre R, Pocock J, Tabrizi SJ

Huntington's disease (HD) is a devastating neurodegenerative disease. It is caused by the presence of an expanded trinucleotide repeat in the HTT gene, resulting in expression of mutant HTT throughout the body. HD patients display a dysfunctional peripheral immune system up to sixteen years before disease onset. This is also shown in HD animal models, where immune system dysfunction is found both in the periphery and CNS. This work aimed to assess the CNS component of the innate immune system, microglial cells, in a human HD model for the first time.

In order to achieve this, a unique cohort of iPSC lines from related individuals with varying expansion lengths (20Q, 56Q, 67Q, 73Q) were differentiated to microglia using an adapted version of Van Wilgenburg *et al.*, 2013. These cells were then subject to a battery of functional tests, to assess the performance of HD microglia with increasing CAG lengths relative to controls.

Our results suggest that HD microglia display altered phenotypes compared to control microglia, in certain functionalities in a Q-length-dependent manner. Specifically, we found a hyper-reactive cytokine response profile upon stimulation with an immune challenge, increased production of ROS, elevated levels of phagocytosis upon stimulation, and reduced viability in the presence of an autophagy inhibitor.

This work represents this first assessment of HD microglia in a human HD model. We have shown that human HD microglia display the same dysfunction found in animal models of HD, and in the peripheral immune cells of patients. Further research is now being conducted to characterise how these dysfunctional HD microglia may affect the health and function of neuronal cell types known to be affected in HD, to ascertain the impact of this dysfunction on disease pathology and progression.

S3-P15

Title: Parallel evaluation of mutant huntingtin and neurofilament light as biomarkers for Huntington's disease: the HD-CSF study

Byrne LM[1], Rodrigues FB[1], Johnson EB[1], Wijeratne PA[2], De Vita E[3,4], Alexander DC[2,5], Czech C[6], Schobel S[6], Scahill RI[1], Heslegrave A[7], Zetterberg H[7,8,9,10], Wild EJ[1]
[1]*Huntington's Disease centre, UCL Institute of Neurology,* [2]*Centre for Medical Image Computing, Department of Computer Science, UCL,* [3]*Lysholm Department of Neuroradiology, National Hospital for Neurology and Neurosurgery,* [4]*Department of Biomedical Engineering, School of Biomedical Engineering and Imaging Sciences, KCL ,* [5]*Clinical Imaging Research Centre, National University of Singapore,* [6]*Neuroscience, Ophthalmology, and Rare Diseases (NORD), Roche Pharma Research and Early Development, Roche Innovation Center Basel, F. Hoffman-La Roche Ltd,* [7]*Department of Molecular Neuroscience, UCL Institute of Neurology,* [8]*UK Dementia Research Institute at UCL,* [9]*Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Mölndal,* [10]*Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital*

Background: Huntington's disease (HD) is a progressive neurodegenerative disorder where there is a pressing need for sensitive biomarkers.

Aims: We assessed mutant huntingtin (mHTT) and neurofilament light (NfL) in parallel.

Methods: CSF mHTT, CSF NfL and plasma NfL were measured using immunoassays in 80 participants (20 healthy controls, 20 premanifest HD and 40 manifest HD) underwent clinical assessments, and standardized CSF and blood collections. Analysis included multiple linear regression models, Pearson's correlations, receiver operating characteristics curves and samples sizes calculations. An event-based model was used to assess the temporal sequence of HD-related biomarker alterations.

Results: CSF mHTT, CSF NfL and plasma NfL were significantly higher as disease progressed. There were significant associations with all clinical measures. Both CSF and plasma NfL were associated with brain volume measures, but CSF mHTT was not. CSF mHTT, CSF NfL and plasma NfL were closely correlated, and highly stable within individuals. CSF mHTT had perfect accuracy for distinguishing between controls and HD mutation carriers, and both CSF and plasma NfL had excellent accuracy for distinguishing between premanifest and manifest HD. Sample size calculations suggest low participant numbers needed to incorporate these measures into clinical trials. The biofluid biomarkers emerged as the earliest detectable alterations in HD, followed by brain volume, motor and cognitive measures.

Conclusion: In this cross-sectional study we provide evidence to support mHTT and NfL as having favourable properties as biofluid biomarkers for HD. Our data suggests that these key biofluid biomarkers are some of the earliest detectable changes in HD.

S3-P16

Title:*NKX6-2* mutations lead to a new distinct disease with spastic ataxia and hypomyelination

Chelban V[1,4], Vandrovcova J[1], Zanetti N[2], Ryten M[6,7], Botía JA[5,6], Bello O[2], Tribollet E[1], Efthymiou S[1], SYNaPS study group, Davagnanam I[8], Wood N[1,3], Houlden H[1,3]
[1]Department of Molecular Neuroscience, [2]Department of Clinical and Experimental Epilepsy, [8]Department of Brain Repair & Rehabilitation, [7]Reta Lila Weston Research Laboratories, Institute of Neurology, UCL.[3]Neurogenetics Laboratory, The National Hospital for Neurology and Neurosurgery.[4]Department of Neurology and Neurosurgery, Institute of Emergency Medicine. [5]Department of Information and Communications Engineering, University of Murcia, [6]Department of Medical & Molecular Genetics, King's College London

Background: Despite advances in genetic testing a large number of hyopomyelinating disorders remain a genetic mystery. We identified a new distinct phenotype of spastic-ataxia with hyopomyelination negative for previously known hyopomyelinating genes.

Methods: In a series of extensively investigated undiagnosed patients, we combined homozygozity mapping, whole exome sequencing, immunoblotting, clinical and neuroimaging analysis for novel gene discovery. Then, using gene expression and network analysis with Weighted Genes Co-expression we placed the new gene within a regulatory pathway.

Results: We mapped this phenotype to deleterious bi-allellic mutations in *NKX6-2* in 14 cases of different ethnic backgrounds providing evidence for a high *NKX6-2* mutation burden in hypomyelinating leukodystrophy disease spectrum. We show that the phenotypic and neuroimaging expression in *NKX6-2* is mutation-specific and that phenotypes with epilepsy in the absence of overt hypomyelination, as well as diffuse hypomyelination without seizures can occur. Our data suggests that the phenotypic consequences of *NKX6-2* mutations is classified in three main subgroups: severe global psychomotor delay with widespread hypomyelination, spastic-ataxia with hypomyelination and spastic-ataxia with seizures. *In-silico* analysis of human brain expression and network data shows that *NKX6-2* is involved in oligodendrocyte maturation and may act within the same pathways of genes already associated with central hypomyelination.

Conclusion: Our study suggests that *NKX6-2* mutations should be considered in patients with autosomal recessive, very early onset of nystagmus, cerebellar ataxia with spasticity and hypomyelination. This syndrome confirms the role of NKX6-2 in myelin homeostasis in the CNS, expanding the genetic causes of spastic ataxia, heterogeneity of developmental genes and inborn errors of myelin metabolism in humans.

S3-P17

Title: Novel loss-of-function mutation in *ACBD5* found in family with ataxia

Roisin Sullivan[1], Emer O'Connor[1], David Lynch[1], Henry Houlden[1]

[1]*Molecular Neuroscience, UCL Institute of Neurology*

Background: Hereditary autosomal recessive cerebellar ataxias are a highly heterogeneous group of disorders that affect the cerebellum and connected regions of the nervous system causing a range of symptoms including uncoordinated voluntary movements. *ACBD5* encodes for the peroxisomal membrane protein Acyl-coA binding domain 5 (ACBD5) which is a peroxisomal membrane protein.

Aims: To investigate the autosomal recessive mutation of *ABCD5* found in a family with ataxia by exploring its pathogenic mechanism and functional effects.

Methods: Blood and skin biopsies taken from consented family members. DNA was extracted from blood and the skin biopsies were used to grow primary fibroblast lines for all family members. Western blots using protein from primary fibroblast lines and anti-ACBD5 antibody were used to confirm type of mutation in the affected family members as well as unaffected, to reveal pattern of inheritance and effect on the protein.

Results: Based on western blots using one affected brother and a healthy control, it appears that there is a loss of function mutation in *ACBD5*, which phenotypically different to previously described cases.

Conclusion: The western blots revealed a novel loss of function mutation in the affected brother, compared to the healthy control which differs phenotypically from previously reported cases of ACBD5-deficiency. Future work will aim to deduce the mechanism using biochemical assays and confocal microscopy to study possible effects on mitochondrial and peroxisomal function.

S3-P18

Title: Genetic investigation of peripheral neuropathy and related disorders using next generation sequencing.

Khan AM[1], Pipis M[1], Vandrovcova J[1], Badarinarayan N[1], Polke J[1], Trabzuni D[1], Reilly MM[1], Houlden H[1]
[1]*MRC Centre for Neuromuscular Disease and Department of Molecular Neuroscience, UCL Institute of Neurology*

Background: Inherited peripheral neuropathies are a group of clinically and genetically heterogeneous disorders, that encompass Charcot-Marie-Tooth disease (CMT), distal hereditary motor neuropathy (dHMN), hereditary sensory neuropathy (HSN), hereditary sensory and autonomic neuropathy (HSAN) and hereditary neuropathy with a liability to pressure palsy (HNPP). Moreover, inherited peripheral neuropathies can be part of a more complex neurological syndrome. The advent of next generation sequencing has allowed the discovery of new disease-causing genes, however, there are patients with peripheral neuropathies remain without a diagnosis and reaching one remains a challenge due to the heterogeneity of the condition.

Aim: To explore the genetic factors of 717 patients with inherited neuropathies who were negative for genes associated with neuropathies.

Patients and Methods: Patients: A cohort of 717 patients with a clinical diagnosis of an inherited peripheral neuropathy and were diagnostically undiagnosed. **Method:** Targeted gene panels involved 15 disease panels. Each panel consist of numbers of genes with maximum numbers 51 and minimum numbers 5, in total 153 genes. 717 Patients were diagnostically investigated with CMT panels only and they were negative. We recruited the sequencing data for 717 patient with involving only disease panels that can cause neuropathy and they were not being investigated diagnostically. A general filtration strategy were performed to prioterize variants associated phenotypes. Such as exclusion common variants with MAF>1% in publically available databases. Synonyms variants, non-coding region variants. Mutations were confirmed and segregated in other family members by Sanger sequencing. A detailed genotype-phenotype analysis was performed in all cases.

Preliminary results: We could solve 7 cases and identify the causative genes. The identified genes are normally cause another neurological disease or other form of CMT. 2 cases with MFN2, 1 cases with NEFL, 2 cases with SACS and 2 cases with NEFH. Neuropathy was the predominant feature in all of these cases. Sanger sequencing is undertaking to confirm the mutation and segregate it in other family members. Analysis is undertaking for the rest of 717 cases.

S3-19

Title: 'GeneLoop': gene therapy activated by seizures to treat epilepsy

Qiu YC[1], Turner T[1], Carpenter J[1], Schorge S[1], Lignani G[1], Kullmann D[1]

[1]*Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology*

Background: Epilepsy is characterized by repetitive seizure episodes, it affects nearly 1 million people worldwide. Approximately 25-30% of patients suffer from drug-resistant epilepsy which cannot be managed satisfactorily by medications.

Aims: For my PhD, I aim to design and test a self-regulatory gene therapy approach using neuronal IEG promoters or/and synthetic activity-dependent promoter derivatives, to target over-excitable neurones, driving a downstream genetic editing mechanism. This 'gene loop' approach will not only have applications in epilepsy, but also other brain diseases characterized by intermittent increases of neuronal activity.

Methods: Standard molecular biology techniques will be used to synthesize appropriate plasmid constructs. *In vitro* characterization**:** Molecular Biology, Patch clamp recordings, network activity analysis with multielectroarrays, Western Blotting, quantitative PCR. *In vivo* characterization: Animal seizure model provides more accurate representation of human epilepsy, and it will provide more details for understanding how 'gene loop' will alter network activities in the brain as well as if it will prevent future seizures.

Results: Preliminary experiments with in vitro primary neuronal cultures show that cfos-kcna1 gene expressing neurons are less prone to spontaneous firing. Cfos promoter transient expression in response to stimulus was shown by immunohistochemistry and GFP-imaging analysis. Electrophysiological characters were investigated with patch clamp recording and multielectro-array recordings *in vitro*.

Conclusion: In summary, this approach is designed to activate only in the presence of overwhelming activity (such as in seizures), and trigger an increase in Kv1.1 channel expression. This will rapidly attenuate neural excitability and raise the threshold for further seizures.

S3-P20

Title: Acute reduction of the Extracellular Trans-Synaptic Protein LGI1 increases network excitability

Lugarà E[1], Chabrol E[1], Lignani G[1], Walker M[1]

[1]*Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology*

Background: LGI1 (Leucine Rich Glioma Inactivated 1) is a secreted trans-synaptic protein, which plays an important role in regulating neuronal communication. Mutations of LGI1 lead to temporal lobe epilepsy in humans and animal models. Autoantibodies against LGI1 have been detected in the serum of patients affected by limbic encephalitis and suffering from epileptic seizures.

Aims: Although LGI1 is strongly implicated in the generation and spread of seizures in genetic and developmental forms of epilepsy, the mechanisms by which LGI1 affects neuronal networks are still debated. My aim is to determine how an acute reduction of LGI1 in the brain leads to epilepsy in rodent models.

Results: For this purpose, I chose and validated a silencing RNA (shRNA) against LGI1. In neuronal cultures, shRNA against LGI1 increased neuronal firing. Local field potential (LFP) of *ex vivo* slices after injection of shRNA-LGI1 in the ventral hippocampus, revealed an increase in the facilitation of mossy fiber to CA3 pyramidal cell neurotransmission.

Conclusion: My results indicate that an acute reduction in LGI1 is sufficient to increase neuronal network excitability. Further studies are planned to determine the mechanisms of this increased excitability and to determine the impact that this has on ictogenesis and epileptogenesis in *in vivo* animal models.

S3-P21

Title: Investigating the pathogenic mechanisms of KCNC1-based progressive myoclonic epilepsy

Heneine J[1], Carpenter J[1], Castaneda MS[1], Schorge S[3], Mannikko R[2], Lignani G[1]
[1]Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, [2]Department of Molecular Neuroscience, UCL Institute of Neurology, [3]Department of Pharmacology, UCL School of Pharmacy

Background: Progressive Myoclonic Epilepsies (PMEs) are a rare and highly heterogeneous group of disorders characterised by myoclonus, tonic-clonic seizures and often ataxia. A recurrent c.959G>A (p.Arg320His) *de novo* mutation in KCNC1, which encodes for the fast delayed rectifier K_v3.1 potassium channel, was recently identified as a significant cause of PME. Functional work in oocytes identified this mutation to be a loss-of-function with a dominant negative effect, when co-expressed with the wild-type K_v3.1 channel. However, when it is overexpressed in neurons, the mutation results in rapid neuronal death. The mechanisms by which this occurs are unknown.

Aims:1)To examine the electrophysiological properties of the pArg320His mutation in K_v3.1 and investigate the possibility of a toxic gating pore leak being introduced in the channel's VSD. 2)To design CRISPR-Cas9 gene editing tools to develop a knock in model for the KCNC1-based PME, which would allow for further characterisation of the mutation.

Methods: Two-electrode voltage clamp recordings of *Xenopus Laevis* oocytes. Design and validation of a CRISPR/Cas9-based HITI tool.

Results: Our results show no detectable gating pore leak current for the homomeric mutant K_v3.1 channel when compared to wild-type and *Shaker* mutant controls. In parallel, we designed and tested 4 sgRNAs targeting our region of interest. The efficiency assay showed effective targeting of Cas9 to the genomic locus of interest.

Conclusion: We have excluded gating pore leak current as a pathogenic mechanism for KCNC1-based PME and now our CRISPR/Cas9 knock-in model will be essential in characterising the mechanisms of K_v3.1-mediated toxicity.

S3-P22

Title: Chemogenetic dissection of the mechanisms of secondary epileptogenesis

Weston M[1], Kullmann D[1]

[1]*Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology*

Background: Epilepsy can be devastating for individuals and presents a huge burden on society. Focal epilepsies acquire treatment resistance over time due to secondary epileptogenesis whereby a primary ictal focus induces a distributed network and secondary independent epileptogenic foci.

Questions: Are secondary epileptogenic foci generated by repetitive seizures from the primary focus during established epilepsy, or do they form independently during induction of epilepsy but mature latently?

Methods: The rat intra-amygdala kainic acid model of temporal lobe epilepsy purportedly induces a primary seizure focus in the ipsilateral hippocampus. EEG from both hippocampi is wirelessly recorded for 6 months. The mutated muscarinic receptor hM4Di, a DREADD (designer receptor exclusively activated by designer drug) responds only to metabolically inert Clozapine-N-Oxide and other ligands. Transduction of excitatory neurons of either primary or secondary ictal foci with hM4Di allows on-demand suppression while preserving brain function elsewhere. Chronically activating optimised hM4Di via depot administration of a novel DREADD agonist should supress epileptic activity, separating the effects of ictogenesis from the effects of repetitive seizures on secondary epileptogenesis.

Results: Generation of the seizure model and chemogenetic optimisation are ongoing. Immunohistochemistry demonstrates DREADD expression in target areas. Initial behavioural assays validate the efficacy of a novel DREADD agonist *in vivo*. Pilot experiments of chronic hM4Di activation in a purported primary epileptogenic focus show a temporary decrease in seizure frequency.

Conclusions: Though optimised DREADD activation by a novel agonist has been validated, sufficient efficacy of hM4Di on focal epilepsy must be shown to answer the project questions.

S3-P23

Title: How bodily physiological signals influence cortical excitability

Khan H[1]

[1]*Sobell Department of Motor Neuroscience and Movement Disorders, UCL Institute of Neurology*

Background: Human cognitive functions and adaptive behaviour depend on neocortical activity and excitability. Disturbances in cortical excitability are related to learning and changes in behaviour. Disturbances in optimal excitability can arise from neurological conditions, like stroke, and are typically associated with many debilitating symptoms. It is imperative to understand what causes disturbances in cortical excitability as this may open the plane to new treatments that may change cortical excitability and help ameliorate neurological symptoms.

Aims: To gain a better understanding of the relationship between cortical excitability and bodily physiological responses.

Methods: Stage 1: Experimental Methods: Approximately 30 healthy volunteers will undergo a battery of assessments for physiological signals to be recorded, these include EEG, EGG, ECG and respiratory rate (RR) measurements. Cortical excitability will be measured using MEPs triggered via TMS. Stage 2: Analytical Methods: Matlab for EEG and EGG (electrogastrogram) signal processing.

Results: The hypothesis being test will be that variability in physiological signals (electrocardiogram, respiratory rate, electrogastrogram) explains variability in cortical excitability measured by motor evoked potentials (MEPs) triggered via TMS. Understanding the place of cortical excitability and its relationship with physiological signals would potentially improve interventional neuromodulatory approaches and consequently improve the recovery of patients affected by cortical excitability disturbances.

Conclusion: The findings will increase our knowledge on the interplay between the body and the brain. They may also open doors to further research into treatments in cortical excitability disturbance.

Keynote Speeches

1- Human stem cell models of dementia

Speaker: Dr Selina Wray

The development of human induced pluripotent stem cells (iPSC) and their subsequent differentiation into neurons has provided new opportunities for the generation of physiologically-relevent in vitro disease models. Despite the advantages they offer to create "disease in a dish" models of tauopathy, there are several challenges associated with their use, particularly the fact that aspects of tau biology such as phosphorylation and splicing are subject to developmental regulation. I will discuss our finding that the developmental regulation of tau splicing is conserved in iPSC-neurons, but disrupted by FTD-associated splicing mutations in MAPT. The developmental phosphorylation of tau is also conserved in our model, and I will discuss our progress using long-term neuronal cultures to understand the earliest pathological changes to tau in cells from patients with mutations in MAPT, APP and PSEN1 in 2D and 3D cultures.

Dr Selina Wray is a research associate in the NIHR BRU for Dementia Research. Selina received her degree in Biochemistry and Biological Chemistry from the University of Nottingham in 2004, before undertaking PhD training in Dr Diane Hanger's laboratory at the Institute of Psychiatry, Kings College London. Selina was awarded her PhD in 2008 and subsequently joined the laboratory of Professor John Hardy at UCL Institute of Neurology as an Alzheimer's Research UK Research Fellow. Her research aims to generate induced pluripotent stem cells and neurons as cell models for neurological disease, with a particular focus on frontotemporal dementia.

2-Active inference and artificial curiosity

Speaker: Professor Karl Friston

This talk offers a formal account of insight and learning in terms of active (Bayesian) inference. It deals with the dual problem of inferring states of the world and learning its statistical structure. In contrast to current trends in machine learning (e.g., deep learning), we focus on how agents learn from a small number of ambiguous outcomes to attain insight. We will simulations of abstract rule-learning and approximate Bayesian inference to show that minimising (expected) free energy leads to active sampling of novel contingencies. This epistemic, curiosity-directed behaviour closes 'explanatory gaps' in knowledge about the causal structure of the world; thereby reducing ignorance, in addition to resolving uncertainty about states of the known world. We then move from inference to model selection or structure learning to show how abductive processes emerge when agents test plausible hypotheses about symmetries in their generative models of the world. The ensuing Bayesian model reduction evokes mechanisms associated with sleep and has all the hallmarks of 'aha moments'.

Key words: active inference · cognitive · dynamics · free energy · epistemic value · self-organization

Professor Karl Friston is a theoretical neuroscientist and authority on brain imaging. He invented statistical parametric mapping (SPM), voxel-based morphometry (VBM) and dynamic causal modelling (DCM). These contributions were motivated by schizophrenia research and theoretical studies of value-learning, formulated as the dysconnection hypothesis of schizophrenia. Mathematical contributions include variational Laplacian procedures and generalized filtering for hierarchical Bayesian model inversion. Friston currently works on models of functional integration in the human brain and the principles that underlie neuronal

interactions. His main contribution to theoretical neurobiology is a free-energy principle for action and perception (active inference). Friston received the first Young Investigators Award in Human Brain Mapping (1996) and was elected a Fellow of the Academy of Medical Sciences (1999). In 2000 he was President of the international Organization of Human Brain Mapping. In 2003 he was awarded the Minerva Golden Brain Award and was elected a Fellow of the Royal Society in 2006. In 2008 he received a Medal, College de France and an Honorary Doctorate from the University of York in 2011. He became of Fellow of the Royal Society of Biology in 2012, received the Weldon Memorial prize and Medal in 2013 for contributions to mathematical biology and was elected as a member of EMBO (excellence in the life sciences) in 2014 and the Academia Europaea in (2015). He was the 2016 recipient of the Charles Branch Award for unparalleled breakthroughs in Brain Research and the Glass Brain Award, a lifetime achievement award in the field of human brain mapping. He holds Honorary Doctorates from the University of Zurich and Radboud University.

PhD talks

1-Acute reduction of the Extracellular Trans-Synaptic Protein LGI1 increases network excitability

Eleonora Lugara, Gabriele Lignani and Matthew Walker

LGI1 (Leucine Rich Glioma Inactivated 1) is a secreted trans-synaptic protein, which plays an important role in regulating neuronal communication. Mutations of LGI1 lead to temporal lobe epilepsy in humans and animal models. Autoantibodies against LGI1 have been detected in the serum of patients affected by limbic encephalitis and suffering from epileptic seizures. Although LGI1 is strongly implicated in the generation and spread of seizures in genetic and developmental forms of epilepsy, the mechanisms by which LGI1 affects neuronal networks are still debated. My aim is to determine how an acute reduction of LGI1 in specific brain circuits leads to epilepsy in rodent models. For this purpose, I chose and validated a silencing RNA (shRNA) against LGI1. In neuronal cultures, shRNA against LGI1 increased neuronal firing. Local field potential (LFP) of ex vivo slices after injection of shRNA-LGI1 in the ventral hippocampus, revealed an increase in the facilitation of mossy fiber to CA3 pyramidal cell neurotransmission. My results indicate that an acute reduction in LGI1 is sufficient to increase neuronal network excitability. Further studies are planned to determine the mechanisms of this increased excitability and to determine the impact that this has on ictogenesis and epileptogenesis both in in vivo animal models and in humans.

2- Huntington's disease phenotypes and disrupted corticostriatal connectivity observed in a novel human iPSC-derived *in vitro* co-culture model.

Caroline S Casey, Yichen Qiu, Matthew P Bentham, Ed Smith, Gabriele Lignani, Ralph Andre, Alison Wood-Kaczmar, Sarah Tabrizi

The corticostriatal (CS) pathway, comprising layer V cortical projection neurons (CPN) and medium spiny neurons (MSN), is one of the first brain pathways to succumb to Huntington's disease (HD) pathology. As a result, disrupted CS connectivity is evident and contributes to the motor and cognitive symptoms experienced by HD patients. Most studies to date elucidating the cellular drivers and mechanisms behind disrupted CS connectivity have originated from HD mouse models and human imaging data. There have been no investigations into the CS pathway using a purely human tissue-derived *in vitro* system. This project utilizes two iPSC lines derived from two closely related individuals; the control line, with 20/20 HTT CAG repeat lengths (20Q), and a juvenile HD line, with 20/73 CAG repeats (73Q). These lines were differentiated in parallel to either MSNs or CPNs, and co-cultured in microfluidic chambers to physically recapitulate the human CS pathway. The co-culture platform was constructed using either 20Q or 73Q iPSC-derived neurons, enabling comparisons between 'healthy' and 'diseased' pathways at a cellular level. Alternatively, crossed co-cultures, where 20Q CPNs synapse onto 73Q MSNs and vice versa, enabled the dissection of neuron-specific pathology and its impact on the CS pathway. High-resolution fluorescence microscopy has revealed the formation of CS synapses within MFC co-cultures, complimented by live cell imaging with calcium binding dye Fluo4, which demonstrates the successful transmission of calcium between neuronal populations within MFCs. Taken together, these data validate this platform as a reliable model of the CS pathway. Moreover, CPN cultures show a HD phenotype in their cytoskeletal dynamics, as axon projection efficiency is drastically reduced in 73Q CPNs compared to 20Q. Furthermore, 73Q MSNs are more susceptible to BDNF-withdrawal induced cell death compared to 20Q cultures. Finally, the intrinsic membrane properties of iPSC-derived MSNs also differ with disease state, as 73Q MSNs are hyper-excitable, with an extended latency to fire and extended refractory period when compared to 20Q MSNs. These results provide a novel insight into the human CS pathway and suggest subtle differences in both the development and function of the CS pathway in HD.

3-Reconciling persistent and dynamic hypotheses of working memory coding in prefrontal cortex

Cavanagh SE , Towers JP , Wallis JD , Hunt LT, Kennerley SW

Background: Working memory (WM) is the temporary holding of information in mind across a delay. It is essential for higher-level cognition and it is impaired in patients with mental illnesses, such as schizophrenia. WM is known to depend upon the prefrontal cortex (PFC), but the neural mechanisms supporting this process are yet to be conclusively determined. One theory, the *"Persistent Hypothesis"*, proposes that single neurons in PFC have sustained firing patterns necessary for WM. A competing explanation, the *"Dynamic Hypothesis"*, argues that the activity of individual neurons is more transient; WM is instead achieved by a time-varying pattern of activity within a whole population of neurons. **Aims**: To reconcile the *"Persistent"* and *"Dynamic"* hypotheses. **Methods**: We analysed single-neuron responses recorded from PFC whilst monkeys performed a spatial WM task, where the reward amount for successful responses varied across trials. Two cues were presented, each followed by a delay. The spatial cue was shown first, and indicated which of 24 locations the subject had to hold in WM. After a delay, the reward cue indicated which of five reward magnitudes the subject would receive for a saccade to the remembered location. **Results**: PFC activity is initially stable and represents the spatial cue (WM contents), consistent with *"Persistent"* theories. However, this stability is lost when the reward cue captures the subjects' attention. Many PFC neurons switched to signalling the reward size, rather than maintaining task-relevant WM information. **Conclusions**: Working memory activity is *"Persistent"* for the most recently presented salient stimulus, but otherwise *"Dynamic"*.

4-Parallel evaluation of mutant huntingtin and neurofilament light as biomarkers for Huntington's disease: the HD-CSF study

Byrne LM, Rodrigues FB, Johnson EB, Wijeratne PA, De Vita E, Alexander DC, Czech C, Schobel S, Scahill RI, Heslegrave A, Zetterberg H, Wild EJ

Background: Huntington's disease (HD) is a progressive neurodegenerative disorder where there is a pressing need for sensitive biomarkers. **Aims**: We assessed mutant huntingtin (mHTT) and neurofilament light (NfL) in parallel.**Methods**: CSF mHTT, CSF NfL and plasma NfL were measured using immunoassays in 80 participants (20 healthy controls, 20 premanifest HD and 40 manifest HD) underwent clinical assessments, and standardized CSF and blood collections. Analysis included multiple linear regression models, Pearson's correlations, receiver operating characteristics curves and samples sizes calculations. An event-based model was used to assess the temporal sequence of HD-related biomarker alterations. **Results**: CSF mHTT, CSF NfL and plasma NfL were significantly higher as disease progressed. There were significant associations with all clinical measures. Both CSF and plasma NfL were associated with brain volume measures, but CSF mHTT was not. CSF mHTT, CSF NfL and plasma NfL were closely correlated, and highly stable within individuals. CSF mHTT had perfect accuracy for distinguishing between controls and HD mutation carriers, and both CSF and plasma NfL had excellent accuracy for distinguishing between premanifest and manifest HD. Sample size calculations suggest low participant numbers needed to incorporate these measures into clinical trials. The biofluid biomarkers emerged as the earliest detectable alterations in HD, followed by brain volume, motor and cognitive measures. **Conclusion**: In this cross-sectional study we provide evidence to support mHTT and NfL as having favourable properties as biofluid biomarkers for HD. Our data suggests that these key biofluid biomarkers are some of the earliest detectable changes in HD.

Aknowledgements

Thank you to everyone presenting posters, giving talks and attending the symposium!

We would especially like to thank:

Our keynote speakers; Professor Karl Friston and Dr Selina

The poster judges

Professor Gabriele Lignani, Professor Stephanie Schorge and Dr Gareth Morris for their talks at the Poster & Presentation workshop

Professor Stephanie Schorge for arranging the 3Rs prize

David Blundred and Sarah Lawson for all of their help in organising the symposium and other events throughout the year.

Our sponsors; Proteintech, Stratech, Addgene, Invicro, Thorlabs, Promega and Abcam

Institute of Neurology