Queen Square Symposium 2017

Abstract Booklet

31st of May 2017

Basement LT

33 Queen Square

London

Poster Numbering

S1: Session 1 (9:30-10:20)

Poster numbers: [S1]: P01-P30

Categories:

- *Cognitive and Behavioural Neuroscience*
- *Imaging*

S2: Session 2 (10:35-11:25)

Poster numbers: [S2]: P01-P30

Categories:

- *Molecular Neuroscience*
- *Animal Research*

S3: Session 3 (11:40-12:30)

Poster numbers: [S3]: P01-P28

Categories:

- *Clinical Neuroscience*
- *Motor Neuroscience*
- *Electrophysiology*

S1: Session 1 (9:30-10:20)

S1-P01

Category: Cognitive & Behavioural neuroscience

Probing the auditory verbal / nonverbal interface in semantic dementia

Sara De Felice, Chris Hardy, Jonathan Rohrer, Jason Warren

Affiliation: Dementia Research Centre, UCL Institute of Neurology

Background: Semantic dementia (SD) is a unique neurodegenerative syndrome characterised by selective temporal lobe atrophy and loss of semantic knowledge. Typically, word meaning is lost before other domains of nonverbal knowledge in SD but it remains unclear how verbal and nonverbal domains interact and whether such interaction might maintain function in the disintegrating semantic system.

Aims: To investigated how verbal and nonverbal domains interact by studying how patients with SD process the interface of verbal (linguistic) and nonverbal (paralinguistic) information in speech signals. My hypothesis was that semantic performance in patients with SD would be better for speech signals where nonverbal information could be engaged versus signals where no such nonverbal cues were available.

Methods: I tested this hypothesis using a novel neuropsychological battery that manipulated lexical stress, onomatopoeic and prosodic cues to meaning in speech recordings.

Results: Preliminary findings suggest that patients with SD show relatively preserved processing of linguistic prosody whereas benefit from other nonverbal cues to spoken word meaning is more variable.

Conclusions: This work has implications for understanding the nature of semantic failure in SD and for developing strategies that could potentially help patients maintain verbal function.

S1-P02

Category: Cognitive & Behavioural Neuroscience

Modifying Beliefs About Performance and Self-Ability Using False Feedback

Marion Rouault[1], Shaima Alsuwaidi[1], Stephen Fleming[1]

Affiliations: [1]*Wellcome Trust Centre for Neuroimaging, UCL*

Background: Metacognition is the ability to monitor one's own cognitive processes, decisions, and actions. Two important aspects of metacognition are task performance and confidence estimates, the latter being a subjective evaluation of the former. While previous literature has focused on how task performance affects confidence, little is known about how confidence is affected by feedback.

Aims: To investigate the influence of feedback on beliefs about performance and self-ability in visual and auditory tasks.

Methods: Human participants will perform a behavioural task in which they will be asked to discriminate the direction of random dot motion or auditory clicks. In 'prime' blocks, participants receive false feedback after their responses to stimuli with no objective direction (null trials). In 'test' blocks, participants don't receive feedback but rate their confidence in their response.

Results: We hypothesize that confidence in 'test' blocks will decrease if the 'prime' block provides negative feedback, and increase with positive feedback. If belief in self-ability is transferable from one modality to another, it is expected to find that 'prime' visual blocks would influence 'test' auditory blocks, and vice versa.

Conclusion: Metacognitive confidence estimates in sensory discrimination tasks might be malleable, under the influence of feedback.

S1-P03

Category: Cognitive & Behavioural Neuroscience

Professional chefs and prospective memory plasticity. Does regular retrieval of delayed intentions enhance prospective memory ability?

Giorgia Cistola, Dr. Sam Gilbert

Affiliation: UCL Institute of Cognitive Neuroscience, London, UK

Background: Recent studies on brain plasticity suggest that expertise influences brain structure and cognitive abilities. For instance studies conducted by Maguire et al (2006) compared taxi drivers and bus drivers on their spatial navigation ability. The results showed differences in hippocampus structure and in neuropsychological tests results between the two professional categories. Similarly, studies on musicians (Gaser and Schlaug, 2003) and bilinguals (Mechelli et al., 2004) showed modifications in brain areas involved in the execution of the respective abilities.

Aim: This study will investigate prospective memory, i.e. the ability to remember delayed intentions. The target population will be professional chefs, who are frequently required to set self-initiated intentions as part of their working life (e.g. remove a pan from the heat in two minutes' time).

Methods: Chefs will be tested using an online test specifically designed for the experiment which lasts approximately 30 minutes. The tasks measure prospective memory, working memory and reasoning abilities. Bartenders will be used as control group.

Expected Results: We predict enhanced time-based prospective memory in chefs.

Conclusions: If predicted results are obtained, this suggests that prospective memory abilities could be enhanced by training procedures.

S1-P04

Category: Cognitive & Behavioural Neuroscience

Atypical Recruitment of Rostral Prefrontal Cortex (BA 10) in Autism Spectrum Disorders: An fNIRS Study of Time-Based, Prosocial Prospective Memory

James E. Crum II[1,2]

Affiliations: [1]Metacognition & Executive Functions Group, UCL Institute of Cognitive Neuroscience [2]Autism Group, UCL Institute of Cognitive Neuroscience

Background: Forming and realizing delayed intentions engage prospective memory (PM), the ability to remember to actuate a thought or behavior in the future, and recruit specific regions of the PFC, notably rostral PFC. Recent research suggests that prospective remembering is improved when delayed intentions are pro-social, as compared to non-social intentions. Pro-social prospective memory (PPM) tasks seldom occur in the absence of the person or people for whom one has an intention. Often others are present to observe one's behavior, and this observation is also often something of which one is aware. Thus, an observer may influence performance on PPM tasks differently than if there is no observer (the audience effect). This effect can be understood in terms of mentalizing processes. How these factors interact in populations that show deficits in mentalizing and prospective memory, namely autism spectrum disorders (ASD), is not well understood.

Aims: The present study therefore aimed to explore the role of rostral PFC (BA 10) in the performance of participants with and without ASD on social and nonsocial prospective memory tasks. Another aim was to investigate whether performance on these tasks will change as a function of the presence or absence of an observer.

Methods: Changes in concentrations of oxygenated and deoxygenated hemoglobin in rostral prefrontal cortex were measured using fiberless, functional near-infrared spectroscopy. Other measures included eye-tracking, heart rate, respiratory rate, and response times.

Results & Conclusions: Pending. Available on poster presenting day

S1-P05

Category: Cognitive & Behavioural Neuroscience

Cognitive Reserve as a Predictor of Clinical and Functional Outcomes Following a First Episode of Psychosis

Andrew Watson[1], Matteo Cella[2], Eileen Joyce[1]

Affiliations: [1]Sobell Department of Motor Neuroscience and Movement Disorders.
[2]Department of Psychology, Instutute of Psychiatry, Psychology and Neuroscience

Background: 'Cognitive reserve' is the capacity of an individual to compensate for brain dysfunction and maintain interpersonal relationships, leisure activities and the ability to work or study. An important index of cognitive reserve (CR) is premorbid IQ which has been shown to directly influence the risk for developing psychosis and functional outcomes in patients diagnosed with schizophrenia.

Aims: To identify CR subgroups in patients presenting with a first episode of psychosis, and determine whether CR predicts 12-month outcome in the patient sample.

Methods: Patients were recruited from Early Intervention Services (EIS) across the UK following a first-episode of psychosis. Hierarchical cluster analysis was used to classify patients into cognitive subgroups based on pre-morbid and current IQ at baseline. Linear mixed models regressions will be used to determine whether cognitive reserve acts as a predictor of clinical and functional outcomes in patients at 12-month follow-up.

Results: The cluster analysis reveals that around the time of development of psychosis, CR declines in a substantial subgroup, whereas in others CR is preserved.

Conclusion: Findings from this study may allow the identification of potential cognitive risk-factors for those at greatest risk of poor-outcome following a first-episode of psychosis and inform targeted and practical interventions to improve outcomes of those with the illness.

S1-P06

Category: Cognitive & behavioural neuroscience

Assessing embodiment using visual priming task

Schone, H[1], Maimon, R[1,2], Makin, T[1]

Affiliations: [1]Institute of Cognitive Neuroscience, Faculty of Brain Science, UCL

[2]FMRIB Centre, Nuffield Department of Clinical Neurosciences, University of Oxford

Background: Cognitive hand priming tasks have been used to identify a negative stimulus-response compatibility effect (Vainio et al. 2011). Through these tasks, we investigate hand representations activated by the visual input of a hand and its effect on motor responses. The paradigm's capacity to recognize and/or test hand prosthesis embodiment can be explored.

Aims: To investigate the mechanisms through which the negative-priming effect works in intact participants, and whether this paradigm could be used to investigate embodiment.

Methods: Response cues were presented for the left and right hands (or feet). Prior to the response cues, left and right priming image of the following categories were presented: 1) hand 2) feet and 3) artificial limbs (cosmetic and hooks). Reaction time and accuracy were measured.

Results: Hand images elicited negative-compatibility effect between prime and response laterality, independent of the effector (hands and feet), while feet images did not elicit priming effects. Finally, prosthetic images (cosmetic or functional) did not elicit the negative-priming effect in 2-handers.

Conclusion: Results from the visual priming tasks suggest that negative-priming effects do not necessarily reflect cognitive embodiment, as previously thought and that more testing is necessary to eliminate confounding visual factors of the results.

S1-P07

Category: Cognitive & Behavioural Neuroscience

Development and validation of a questionnaire on laughter production and perception

Muller M[1], Lima CF[2], Tuarek A, Scott S[1]

Affiliations: [1]Institute of Cognitive Neuroscience, University College London
[2]Faculty of Psychology and Education Sciences, University of Porto

Background: Laughter is a complex social emotion and an important form of non-verbal communication. Humans vary widely in their production and perception of laughter.

Aim: The development and validation of a questionnaire on laughter production and perception.

Methods: Principal Components Analyses (PCAs) were conducted to reduce a large number of items to a well-structured questionnaire and to find principal components that describe laughter behaviour. Three experiments were designed to validate the questionnaire.

Results: A 60-items questionnaire was reduced to a 30-items questionnaire. The PCA resulted in a four-components solution, describing frequency, understanding, usage, and liking of laughter.

Conclusion: Inter-individual differences in laughter production and perception can be described on four distinct components. Now, the validity of the questionnaire has to be shown, i.e. that the questionnaire can predict actual laughter behaviour.

S1-P08

Category: Cognitive & Behavioural Neuroscience

High-dimensional therapeutic inference in the focally damaged human brain

T. Xu [1], R. Jager [1], M. Husain [2,3], G. Rees [1,3,4,5], P. Nachev [1]

Affiliations: [1] Department of Brian repair and rehabilitation, Institute of Neurology, UCL, London, WC1N 3BG, UK.
[2] Department of Clinical Neurology, University of Oxford, Oxford OX3 9DU, UK.
[3] Institute of Cognitive Neuroscience, UCL, London WC1N 3AR, UK.
[4] Faculty of Life Sciences, UCL, London, WC1E 6BT, UK.
[5] Wellcome Trust Centre for Neuroimaging, UCL, London WC1N 3BG, UK.

Background: the conventional low-dimensional inference to be highly insensitive to therapeutic effects, which is partial causes of the failure to replicate in human's positive interventional effects in experimental animals. High-dimensional models, by contrast, dramatically improve therapeutic inference by leveraging complex individuating patterns in the functional architecture of the brain. This may force a re-evaluation of therapeutic inference in the human brain.

Aims: High-dimensional modelling of the focally damaged human brain was established to reveal substantial therapeutic effects opaque to current low-dimensional approaches.

Methods: High-dimensional models derived from the processed large-scale (n=1172) clinical MRI and CT imaging associated with the technology of machine learning were adopted to identify the relationships with brain damage and patient clinical outcomes.

Results: A high-dimensional model where the pattern of focal damage is adequately parameterized detected an intervention effect more accurately. The quantity of the impacts was 56.0% versus 62.9%, and 55.0% versus 78.4% on non-lesion altering and lesion altering simulations, respectively.

Conclusion: though the benefit from high-dimensional modelling is bound to vary with the behavioural outcome studied, it can only be greater the more distributed the underlying critical functional architecture. The deepening appreciation of the fundamentally interconnected nature of the brain points decisively towards a need for greater, not lesser, complexity in our explanatory models. Therapeutic inference must inevitably reflect this; moreover, the payoff is not only a greater understanding of the brain but potentially the correct appreciation of many treatments hitherto erroneously thought to be ineffective.

S1-P09

Category: Cognitive & Behavioural Neuroscience

Visuomotor integration in Insight46, a neuroscience sub-study of the MRC National Survey of Health and Development

Kirsty Macpherson [a], Jennifer M Nicholas [b], Elizabeth R Donnachie [a], Jessica Collins [a], David M Cash [a], Jana Klímová [a], Sebastien Ourselin [a], Christopher A S Lane [a], Thomas Parker [a], Heidi Murray-Smith [a], Andrew Wong [c], Sebastian J Crutch [a], Susie M D Henley [a], Nick C Fox [a], Marcus Richards [c†], Jonathan M Schott [a†]
[†] joint senior authors

Affiliations: [a]Dementia Research Centre, Department of Neurodegenerative Diseases, UCL Institute of Neurology; [b]Department of Medical Statistics, London School of Hygiene and Tropical Medicine; [c]MRC Unit for Lifelong Health and Ageing at UCL

Background: Alzheimer's Disease (AD) and other dementias are a huge public health problem and currently lack effective treatments. A greater understanding of the long pre-symptomatic phase of AD is urgently needed. Among other factors this involves subtle cognitive decline, including evidence of impaired visuomotor integration.

Aims: We aimed to describe the psychometric properties of a circle-tracing task using Insight46, a neuroscience sub-study of the MRC National Survey of Health and Development (British 1946 birth cohort, now aged 71), and to test the hypothesis that performance will be associated with amyloid deposition, a potential biomarker of preclinical AD.

Methods: To date, 235 participants have been assessed. Six circle-tracing trials were administered, half with direct visual feedback and half with indirect visual feedback, with concurrent serial subtraction. Outcomes include tracing speed and accuracy. GEE models were used to investigate the predictive effects of age at assessment, gender and childhood cognitive ability, and to compare performance of amyloid-positive and amyloid-negative groups.

Results: Consistent with previous studies, participants found the indirect condition more difficult. Predictors of faster tracing speed were male gender and older age at assessment, whereas predictors of tracing accuracy were younger age at assessment and higher childhood cognitive ability.

Conclusions: These results point to interesting speed-accuracy trade-offs that merit further exploration. There is no evidence of any associations with amyloid deposition. Future work will explore relationships with other potential biomarkers of preclinical AD and investigate longitudinal change on the circle-tracing task after two years.

S1-P10

Category: Cognitive & Behavioural Neuroscience

Basic Information Processing Characteristics Associated with Extreme Political Beliefs and Dogmatism

Max Rollwage[1,2], Ray Dolan[1,2], Steve Fleming[1]

Affiliations: [1]Wellcome Trust Centre for Neuroimaging, University College London, London WC1N 3BG,United Kingdom
[2]Max Planck University College London Centre for Computational Psychiatry and Ageing Research, London WC1B 5EH, United Kingdom

Background: Dogmatism is characterized by a “relatively unchangeable, unjustified certainty” in one’s belief systems (Altemeyer, 1996) and has been hypothesized as underlying feature of political extremism. This indicates that extreme political beliefs might be associated with characteristics of basic information processing, related to confidence, the insight about correctness of own beliefs (metacognitive ability) and the integration of new evidence into existing beliefs.

Aim: We are interested whether extreme political beliefs and dogmatism are associated with those basic information processing characteristics.

Methods: We conducted a web-based study, assessing political orientation and dogmatism via questionnaires. In addition, participants conducted a perceptual decision task which was either directly followed by a confidence rating or by additional evidence presentation before the confidence rating. The behavioral paradigm was used for assessing overconfidence, post-decision evidence integration and metacognitive ability.

Results: As predicted, on questionnaire level, participants with extremer political beliefs were more dogmatic. Behaviorally, metacognitive ability predicted the extent of post-decision evidence integration. Interestingly dogmatism was negatively associated with metacognitive ability and also with post-decision evidence integration, while extremeness of political beliefs was only associated with post-decision evidence integration. Moreover, the association between post-decision evidence integration and political extremeness was mediated by dogmatism.

Conclusion: Our results indicate that very general information processing characteristics are associated with dogmatic world views, potentially contributing to this high-order attitude, which is itself predictive of political extremeness.

S1-P11

Category: Cognitive & Behavioural Neuroscience

Rehumanizing The Homeless: Altered BOLD Responses Following Contact With An Extreme Out-Group

Kirk, P. A.[1], & Harris, L. T. [2]

Affiliations: [1]Institute of Cognitive Neuroscience, University College London.
[2]Department of Experimental Psychology, University College London.

Background: Dehumanized perception is a product of denying others mental states. Evidence has accumulated to suggest many individuals do not spontaneously attribute mental states towards those who are perceived to be low in warmth and competence. Specifically, social groups such as the drug addicted and homeless have been found to elicit differential BOLD responses in the social cognition network.

Aims: To investigate the flexibility of neural responses to the homeless as a product of contact.

Methods: Participants viewed images of 8 different social groups during fMRI. Scans were collected before and after interacting with homeless individuals in a soup kitchen.

Results: Currently being analysed.

Conclusion: N/a.

S1-P12

Category: Cognitive & Behavioural Neuroscience

Verbal Fluency in PSP

Chowdhury S[1], Foley J[1].

Affiliations: [1] Department of Neuropsychology, National Hospital for Neurology & Neurosurgery [2]Clinical Neurology, UCL Institute of Neurology

Background: Although verbal fluency is reduced in PD, it is strikingly impoverished in PSP. This may reflect the more marked subcortical pathology leading to greater functional frontal deactivation in PSP. If this is the case, patients with PSP should demonstrate greater evidence of executive dysfunction on measures of verbal fluency, with fewer words, higher frequencies and reduced clustering.

Aims: To analyse the different components of verbal fluency in patients of PSP, Parkinson's disease and healthy control and correlate with the performance on measures of executive function.

Methods: 11 Patients of PSP, 30 patients of PD and 40 healthy individuals underwent tests of verbal fluency and executive function. Performance on these tests will be analysed to reveal number, length and frequency of words produced on measures of verbal fluency, alongside any evidence of clustering and switching. These verbal fluency parameters will be correlated with performance on measures of executive function

Results: The research is still ongoing and we are yet to reach a quantitative result.

Conclusion: It is expected that analysis of verbal fluency parameters will shed light on the executive contributions to the verbal fluency impairment in PSP

S1-P13

Category: Cognitive & Behavioural Neuroscience

Sensitivity to Social Cues in Autism Spectrum Conditions

Suddell S F[1], Forbes P A G[1], Hamilton A F[1]

Affiliations: [1]UCL Institute of Cognitive Neuroscience

Background: Autism Spectrum Conditions (ASC) are characterised by difficulties in social interaction. This is in part believed to originate from a failure to utilise social information to modulate their behaviour. Typically developed (TD) individuals often unconsciously mimic others actions, but this behaviour is believed to be impaired in ASC.

Aims: To investigate whether TD and ASC individuals differ in how they alter their choices and physical movements in response to subtle social information.

Methods: ASC and TD participant's choices and movements were compared in an offline vs. social setting (using a virtual reality avatar). 80 pairs of images were presented in each condition and participants indicated their preference. Both the avatar and participant chose by physically pointing, and participant's movements were recorded with an electromagnetic marker. The avatar varied her direction and height of pointing.

Results: Data will soon be analysed. It is hypothesised that, in comparison with typical participants, ASC participants will show a reduced tendency to mimic the avatars movements during the social condition.

Conclusion: This study will further elucidate the exact nature of social impairment in ASC by exploring how subtle social cues influence their behaviour.

S1-P14

Category: Cognitive & Behavioural Neuroscience

First predominant behavioural symptoms in AD and their neuroanatomical correlates

Jimenez D[1,2], Fiford C[3], Barnes J[3]

Affiliations: [1]Dementia Research Centre,, UCL Institute of Neurology, London, UK
[2]Department of Neurological Science, Faculty of Medicine, University of Chile, Santiago, Chile

Background: Behavioural or neuropsychiatric symptoms (NPSs) affect more than 80% of patients with Alzheimer´s disease (AD) and have a negative impact on cognitive, functional and social outcomes. The most commonly reported first behavioural symptoms in AD are apathy/withdrawal, depression and irritability. However, relatively little is known about the specific neurobiology of different NPS profiles.

Aims: The aim of this study is to determine structural atrophy correlates of first predominant behavioural symptoms in AD.

Methods and patients: An observational, retrospective and cross-sectional study is being performed using the National Alzheimer´s Coordinating Center (NACC) data set collected from United States National Institute on Aging-funded Alzheimer´s disease centers (ADC). Subjects were diagnosed with probable or possible AD according to accepted diagnostic criteria and first predominant behavioural symptoms were registered by the clinicians at the first visit as depression, apathy, irritability or no symptoms. Structural analysis of brain MRI images will focus on grey matter differences using voxel-based morphometry (VBM).

Results: 136 patients have accomplished image quality criteria for VBM analyses. On average, patients were 74.5 ±10.1 years old at scan (range 43-94 years) and 79 (58%) are female. By using general linear models, we will assess differences in atrophy patterns independent of age, gender, symptoms lenght and head size. Based on previous studies, we hope to identify the involvement of specific frontal regions and fronto-temporal-subcortical networks.

Conclusions: Since behavioural symptoms are associated with atrophy patterns in AD, this study could contribute to our understanding of neurobiology underpinning specific NPSs.

S1-P15

Category: Cognitive & Behavioural Neuroscience

Feeling Space with teeth: a psychophysical study

Bono D[1], Haggard P[1]

Affiliations: [1]UCL Institute of cognitive Neuroscience

Background: Periodontal Mechanoreceptors (PDLMs) are sensory receptors that exert a role in the transmission of information about the point of attack, the force applied on a given tooth and the direction of tooth loading.

Aims: The present study aims to investigate whether Periodontal Mechanoreceptors (PDLMs), can sense spatial features of tactile stimuli delivered on a given tooth, in addition to their established role in sensing force applied to teeth.

Methods: Linear tactile stimuli of four different length (2,4,6 and 8 mm) were delivered over the facial surface of the participant's maxillary central incisor with a mechanical arm. Participants were asked to classify the stimuli as long or short according to their perceived length.

Results: Cumulative Gaussian functions were fit to each participant's data with least-squares regression. The probability of "Long" answers is <30% for short stimuli (2 and 4 mm) and >60% for long stimuli (6 and 8 mm).

Conclusion: This is the first evidence of a capacity for spatial perception on teeth. In particular, humans are able to discriminate the spatial extent of a tactile stimulus moving across the tooth surface. Consequently, force sensitivity of Periodontal Ligament Receptors may also explain spatial perceptual capacity of teeth.

S1-P16

Category: Cognitive & Behavioural Neuroscience

Effects of sleep and reward on the neuronal representation of a graph network

Bernard M. [2], Feld G.B.[1], & Spiers H.J.[1]

Affiliations: [1]Spatial Cognition Group, UCL Institute of Behavioural Neuroscience
[2] MSc Brain and Mind Science, UCL Institute of Neurology

Background: Neural representations in the brain are strengthened to stabilize and preserve memories during deep slow-wave sleep. This effect is especially effective for relevant information such as rewarded memories.

Aims: To investigate the impact of sleep and reward on associative memory representations in the human brain by using an associative memory task of stimuli arranged in a network. Measuring brain responses to these stimuli after a period of consolidation by fMRI.

Methods: Participants will be asked to memorise a network of associated stimuli during a learning task by moving to neighbouring stimuli as fast and as accurately as possible. Some of the stimuli are paired with rewards. During the retention interval participants either sleep or are sleep-deprived. Retrieval is tested outside (for behaviour) and inside the scanner (for brain activation). Sleep and sleep-deprivation are applied a balanced cross-over within-subject design.

Results: The data collection will begin soon. However, through the piloting of the data, it was possible to assess that participants could learn and remembered the network with an overall accuracy of 60% of hit-rate during the retrieval. At the moment, no piloting has been done for the fMRI.

Conclusion: It is expected that sleep and reward influence the retention of memory. Moreover, the research plans to replicate the findings that associative memory relies on the hippocampus and that the ventral striatum provides reward information. We assume the structure of the learned network can be reconstructed from the brain data and the behavioural data, but is distorted around rewarded nodes.

S1-P17

Category: Cognitive & Behavioural Neuroscience

EEG and Pupil Dilation in Response to Familiar and Unfamiliar Music

Jagiello R[1,2], supervised by Chait M[1], & Pomper U[1]

Affiliations: [1]The Ear Institute, UCL Faculty of Brain Sciences
[2]UCL Institute of Neurology (MSc Brain and Mind Sciences)

Background: Music recognition and processing may be mediated by degrees of familiarity, liking and emotional relevance of the song in question.

Aims: To investigate differences in ERPs and pupil size in response to familiar as compared to unfamiliar songs, special focus being laid in regard to temporal aspects of music recognition.

Methods: Main subjects (N = 10) filled out a music questionnaire detailing their favourite and most familiar songs. The latter were matched to tracks that are both similar and unknown to the participant. A song pair was then dissected into chunks of 750ms and strung together into a single track with gaps of 1000ms.The resulting tracks are played to participants while EEG, as well as pupil dilation responses are recorded. Contrary to the main group who remains to be tested, data from controls (N = 12), who did not know any of the songs, was already recorded in order to verify the song matching process.

Results: Within the control group no differences in overall averages of ERPs as well as pupil size were found between familiar and unfamiliar conditions. Early pilot data (N = 2) for test subjects reveals a rapid differentiation (N100) between both conditions. More data needs to be gathered to draw firm conclusions regarding the occurrence of this effect.

Conclusion: Overall, the song matching process showed itself successful, excluding the possibility that a particular musical characteristic acts as a confound in a recognition effect, that is potentially detected once recordings within the main group are complete.

S1-P18

Category: Cognitive & Behavioural Neuroscience

Predicting functional properties of prefrontal cortex neurons using resting activity patterns

John Towers, Sean Cavanagh, Steven W. Kennerley

Affiliations: Sobell Department of Motor Neuroscience and Movement Disorders; UCL Institute of Neurology

Background: Prefrontal cortex (PFC) neurons exhibit heterogeneity in both task-related selectivity and autocorrelation of resting activity. The temporal decay in the autocorrelation of resting neuronal activity may reflect a capacity to sustain and integrate information over time.

Aims: To investigate whether a long-decaying autocorrelation in resting activity is predictive of whether a neuron will encode task-variables reflecting temporal integration processes.

Methods: Single neuron recordings were obtained from 4 PFC areas in macaque monkeys performing a spatial working memory task. Cues for spatial location and reward volume were separately presented with intervening delay periods. Neuronal selectivity for reward-value and spatial-location were analysed separately across the trial. An exponential decay function was fitted to each neuron's resting activity, and correlated with spatial and reward selectivity.

Results: Neurons in both ventrolateral PFC (VLPFC) and anterior cingulate cortex exhibited strong coding of reward information compared to neurons in orbitofrontal cortex and dorsolateral PFC. Spatial information was predominantly encoded by VLPFC. Moreover, VLPFC neurons exhibited sustained coding of both reward and spatial information across delays until such information could be integrated. Reward and spatial information encoding was positively correlated with longer temporal decay parameters.

Conclusion: Characterising resting firing rate structure can be predictive of whether a neuron will encode working memory correlates. The results found in this study also support the "persistent firing in delay" theory of working memory.

S1-P19

Category: Cognitive & Behavioural Neuroscience

Does Choice Confidence in Perceptual Decision-Making Leak to Value-Based?

Metin Ozturk, Dr. Benedetto de Martino

Affiliations: UCL Institute of Cognitive Neuroscience

Background: Choice confidence has been demonstrated to leak from one perceptual task to another (i.e., high confidence in initial perceptual task caused higher confidence in the following one). It has been shown right rostrolateral PFC involved in formation of metacognitive judgements in perceptual and value-based decision-making tasks. Its neuronal connectivity with occipital lobe during perceptual decision-making tasks and ventromedial PFC during value-based ones posit whether it is a domain-general region for choice confidence to form metacognitive representations from object-level information.

Aims: It has been investigated whether choice confidence in a perceptual task will significantly influence choice confidence in a value-based decision-making task. Additionally, it has been investigated whether metacognitive sensitivity is stable across domains. Finally, it has been studied how metacognitive sensitivity in perceptual and value-based decision-making tasks interact with learning rates in value-based task.

Methods: Visual stimuli such as random dot kinematograms were created and presented on computer. Behavioral methods were adopted such as measuring confidence by visual analogue scale and reaction time. Computational modelling approach was adopted to analyze data.

Results: It has been expected that there will be confidence leak, metacognitive sensitivity will be relatively stable across domains and higher metacognitive sensitivity will result as a higher learning rate.

Conclusion: A domain-general mechanism for forming choice confidence has been expected to be demonstrated with its relation to reinforcement learning models

S1-P20

Category: Imaging

Pathological correlates of white matter hyperintensities on cadaveric MRI in progranulin-associated frontotemporal dementia

Ione OC Woollacott[1], Martina Bocchetta[1], Carole H Sudre[1,2], Basil H Ridha[3], Catherine Strand[3], Robert Courtney[3], Sebastien Ourselin[1,2], Jorge M Cardoso[1,2], Jason D Warren[1], Martin N Rossor[1], Nick C Fox[1], Tamas Revesz[4], Tammaryn Lashley[4], Janice L Holton[4], Jonathan D Rohrer[1]

Affiliations: [1]Dementia Research Centre, Department of Neurodegenerative Disease, UCL Institute of Neurology, London, UK
[2] Translational Imaging Group, Centre for Medical Image Computing, University College London, London, UK
[3] NIHR Queen Square Dementia Biomedical Research Unit, Institute of Neurology, University College London, London, UK
[4] Queen Square Brain Bank, Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK

Background: White matter hyperintensities (WMH) are present on magnetic resonance imaging (MRI) brain scans of patients with frontotemporal dementia (FTD) associated with progranulin (*GRN*) mutations. Their histopathological correlates are unknown. Cadaveric MRI brain scanning enables precise correlation of neuroimaging abnormalities with histology in post-mortem brain tissue.

Aims: We investigated the histopathological correlates of WMH in a patient with *GRN*-mutation associated behavioural variant FTD who underwent cadaveric MRI and post-mortem analysis.

Methods: The patient had an *in vivo* MRI 2.6 years before death and cadaveric MRI within 24 hours after death. Five brain regions underwent detailed histopathological analysis, corresponding to areas of severe or absent WMH on cadaveric MRI. Histological examination was performed using haematoxylin and eosin, Luxol fast blue and Perl stains and immunohistochemistry for TDP-43, Aβ, phosphorylated neurofilament, myelin basic protein and glial fibrillary acidic protein. Vascular pathology was semi-quantitatively assessed using recommendations of the Vascular Cognitive Impairment Neuropathology Guidelines.

Results*: In vivo* and cadaveric MRI showed progressive, asymmetric frontotemporal and parietal atrophy, and asymmetric WMH, predominantly affecting frontal white matter. Brain regions with most severe WMH on MRI (frontal pole and anterior frontal lobe) displayed most severe cortical and white matter pathology (neuronal loss, spongiosis, gliosis, demyelination and TDP-43). However, there was no or minimal vascular pathology in regions with WMH.

Conclusion: Vascular pathology does not underlie extensive WMH in *GRN*-mutation associated FTD. Given the role of *GRN* in inflammatory pathways, excessive inflammation and demyelination could lead to WMH, or axonal degeneration secondary to cortical neuronal loss.

S1-P21

Category: Imaging

The role of within-subject stress on the neural substrates of working memory encoding and retrieval

Michele Garibbo

Affiliations: Oliver J Robinson

Background: Altered learning and memory processes are common in stress-related disorders, contributing to the maintenance of symptoms and everyday functioning difficulties. Our recent behavioural work showed that threat of shock (i.e. translational method to induce stress) may selectively impair the encoding of facial stimuli, but improve spatial working memory performance in a state dependent manner.

Aims: The present study aims to extend these findings into a fMRI paradigm in the attempt to understand the neural circuitry responsible for the interactions between memory functions and stress.

Methods: Approximately 50 healthy participants will perform a facial recognition and a spatial working memory task inside an fMRI scanner, under conditions where they are at risk of unpredictable foot shock or a control condition where they are safe from shock. In both tasks, the risk of shock will be manipulated within-subjects and across both the encoding and the retrieval of the memory stimuli.

Results: We predict that structures involved in threat processing (e.g. amygdala & mPFC) will overlap and compete with the extensive network involved face processing, explaining the behavioural impairments in the encoding of faces while being at risk of shock.
In the spatial task, threat processing may lead to greater coupling between hippocampal and para-hippocampal areas across encoding and retrieval, accounting for the improvement in behavioural performance when threat was induced at both encoding and retrieval.

Conclusion: These findings will contribute to the growing literature on the neural circuits underlying stress-related disorders and, ultimately, the development of biologically informed treatments.

S1-P22

Category: Imaging

Optimizing functional connectomics in neurodegeneration using machine learning and modularity

Jonathan Vanhoecke[1], Peter McColgan[1]

Affiliations: [1]Department of Neurodegenerative Disease, Institute of Neurology, UCL

Background: Connectomics can be used to investigate functional brain networks in neurological diseases such as schizophrenia, Alzheimer's and Huntington's disease (HD). In this developing field, different connectome construction approaches have emerged in parallel. However, there is a need to understand the subsequent influences of different approaches when constructing the connectome.

Aims: This study aims to systematically compare connectome construction approaches based on their biological relevance to functional networks in neurodegeneration. The research question is twofold: Which functional connectome construction is most sensitive to discriminate HD gene carriers from healthy controls? How does functional connectome construction affect modular organisation?

Methods: We assess the effect of the construction approach in resting-state fMRI networks, using machine learning and modularity. The considered factors are bandpass-filtering versus wavelet decomposition for physiological noise correction, weighted versus binarised networks, and unthresholded versus proportional thresholded networks. The systematic comparison is performed across three parcellation atlases (structural, functional and multi-modal).

Results: Bandpass-filtering generates the most sensitive connectome construction, while binarisation and proportional thresholding does not increase sensitivity. Multi-modal and functional parcellation atlases yield a higher discrimination rate between HD and controls. Modular organisation is not affected by binarisation or thresholding, while a coarse-grained atlas may generate more consistent modular organisation compared to fine-grained atlases.

Conclusion: For functional connectomics, this study suggests that construction approaches making use of weighted, unthresholded connectivity matrices are outperforming other approaches, and the use of functional or multi-modal parcellation atlases is recommended.

S1-P23

Category: Imaging

Vascular Risk and The Anatomy of Tissue Loss

Putri Widya Andini, Cassidy M Fiford, and Josephine Barnes for the Alzheimer's Disease Neuroimaging Initiative*

Dementia Research Centre, Department of Neurodegenerative Disease, UCL Institute of Neurology, London, UK

**Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analyses or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf*

Background*:* Recent studies support the idea that vascular risk factors (VRF) are related to the mechanisms of Alzheimer's Disease (AD). There is also evidence that the most important gene associated with increased risk of AD (APOE e4) is also associated with increased vascular disease.

Aims: The study will investigate the independent relationships of VRF with longitudinal brain atrophy.

Methods: Data comprised of 193 controls, 332 mild cognitive impairment (MCI), and 149 AD subjects. Scans were registered using the Longitudinal Toolbox in the Statistical Parametric Mapping software (SPM12), and the resultant Jacobian maps underwent Voxel Based Morphometry. A marginal model will be fitted using the Sandwich Estimator toolbox, with main effects of group and each VRF, to assess the association of volume changes to the specified risk factors (APOE e4, blood pressure, serum glucose, cholestrol, stroke, BMI, hypertension, diabetes, hypercholesterolemia, smoking, heart disease, stroke-related condition, peripheral arterial disease, and white matter hyperintensity volume). Analyses are adjusted for total intracranial volume. Results are significant at $p<0.05$ with correction for multiple comparisons.

Results: There was a relationship of APOE e4 with increased atrophy, particularly affected bilateral precuneus, occipital, and temporal lobes. Subsequent analyses will be performed separately for other VRFs.

Conclusion: Presence of APOE e4 is related to significant posterior brain atrophy, the remaining VRF are yet to be investigated.

S1-P24

Category: Imaging

Improved MRI T2 mapping using maximum likelihood estimation

N Zafeiropoulos[1,2], RL Janiczek[3], TA Yousry[1,2], E De Vita[1], JS Thornton[1,2].

Affiliations: [1]Neuroradiological Academic Unit, UCL Institute of Neurology, London, UK; [2]MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, London; [3]GlaxoSmithKline, London, UK.

Background: MRI T2 relaxometry is sensitive to pathology in many conditions. It is commonly implemented by fitting a single or multi component exponential to the multi-echo signal using least-squares minimization. Limitations with this approach include additional processes besides simple exponential transverse-magnetization decay contributing to the signal behaviour e.g. stimulated and alternate echo effects. Also, the assumptions of normally distributed and homoscedastic noise implicit in the least squares minimization often break down in reality.

Aims: To address these limitations using the extended phase graph formalism (EPG) to more adequately model the signal behaviour and maximum likelihood model parameter estimation (MLE) accounting for the Rician noise distribution in MRI.

Methods: Simulations tested the applicability of this approach, by generating multiple replicates with varying levels of added noise, estimating EPG model parameters in each case using MLE. Phantom data provided validation.

Results: Fitting the EPG model to simulated and phantom data yielded accurate T2 estimates even in the presence of Rician noise. E.g, for simulations with acquisition conditions matching the phantom experiments (ground-truth T2=37.8ms, T1=460ms, refocusing angle = 2 x excitation angle = 66.5°, signal at t=0 = 3567.5 units, 17 echoes with 9.9ms spacing; noise standard deviation in the real and imaginary channels = 36 units) for 113 simulated replicates MLE-estimated T2 was 37.4 ± 1.4ms (mean ± SD).

Conclusions: Improved tools for CPMG T2 estimation have been developed. The next stage will be application *in vivo* to assess the value of muscle-water T2 as a trial outcome measure in neuromuscular diseases.

S1-P25

Category: Imaging

A resting state fMRI study of cognitive performance in patients with a clinically isolated syndrome suggestive of multiple sclerosis

Marta Batlle-López, Adnan Alahmadi, Sara Collorone, Ferran Prados, Claudia Wheeler-Kingshott, Olga Ciccarelli, Carmen Tur

Affiliations: Department of Neuroinflammation, UCL Institute of Neurology

Background: Cognitive impairment has been seen in multiple sclerosis (MS), even from early stages of the disease, and has been related to structural brain damage. Conventional MRI markers can only partly explain cognitive dysfunctions. In this context, functional connectivity analysis performed with resting-state fMRI data has emerged as a promising tool to evaluate the underlying pathophysiology of cognitive dysfunction in MS, since abnormal functional connectivity patterns seem to reflect compensatory mechanisms that limit clinical manifestations caused by structural brain damage at the early stages of MS.

Aims: The objectives of this study are 1) to describe the resting-state networks observed in patients with a clinically isolated syndrome (CIS), e.g. with a first inflammatory-demyelinating episode suggestive of MS, and compare them with those obtained in a group of healthy controls; 2) to examine the association between resting-state networks and cognitive performance in the CIS group.

Methods: Thirty-one resting-state fMRI scans have been undertaken (19 CIS and 12 controls) and clinical data (e.g. cognitive and disability scores) has been obtained for the CIS group. Independent component analysis will be done with CONN toolbox.

Results: We expect to obtain differences in resting-state networks between the two groups, especially in cognitive-related networks.

Conclusion: Resting-state fMRI studies in CIS patients could give us an important insight on the underlying pathophysiology of cognitive dysfunction in MS.

S1-P26

Category: Imaging

Length of white matter connections determine their rate of atrophy in premanifest Huntington's disease

Peter McColgan (1), Kiran K Seunarine (1), Sarah Gregory (1), Adeel Razi (1), Marina Papoutsi(1), Jeffery D. Long (2), James A. Mills (2), Eileanoir Johnson (1), Alexandra Durr (3), Raymund AC Roos (4), Blair R Leavitt (5), Julie C. Stout (6), Rachael I Scahill (1), Chris A Clark(1), Geraint Rees (1), Sarah J Tabrizi (1) and the Track-On HD Investigators

[1]. University College London, UK
[2]. University of Iowa, USA
[3]. University Hospital Pitié-Salpêtrière, France
[4]. Leiden University Medical Centre, The Netherlands
[5]. University of British Columbia, Canada
[6]. Monash University, Australia

We lack a mechanistic explanation for the stereotyped pattern of white matter loss seen in Huntington's disease. While the earliest white matter changes are seen around the striatum, within the corpus callosum and in the posterior white matter tracts, the order in which these changes occur and why these white matter connections are specifically vulnerable is unclear. Here we use diffusion tractography in a longitudinal cohort of individuals yet to develop HD to identify a hierarchy of white matter connection vulnerability, where cortico-striatal connections are most affected, followed by inter-hemispheric and intra-hemispheric connections. We provide a mechanistic explanation for this hierarchy by showing that the physical length of white matter connections between a brain area and its neighbours predicts the rate of atrophy over 24 months. This finding demonstrates a new principle underlying neurodegeneration in Huntington's disease, whereby the longest brain connections are the first to suffer damage that can account for the stereotyped pattern of white matter loss observed in premanifest Huntington's disease.

S1-P27

Category: Imaging

Putamen lesions and aphasia: the relationship and outcome post stroke

Griffin O[i] ,Price CJ[ii]

Affiliations:[1] Department of Stroke Medicine, Institute of Neurology, University College London, 2 Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London

Background: Previous longitudinal studies have identified that at least 25% of strokes are subcortical infarcts.(Wolfe et al., 2002) There is limited data available on putamen only lesions and their involvement in language. This is a novel investigation.

Aims:

1. Does left putamen infarction that preserves other known language regions, impair speech production more than comprehension?
2. What type of speech production deficit is encountered in those who have putamen lesion?
3. Is speech recovery after left putamen damage faster than damage to other known language regions?

Methods/Materials/Patients: The PLORAS (Predicted Language Outcome and Recovery After Stroke) database (n=916) and in-house software were used to identify two groups of right handed, English speaking patients with data collected 1-10 years post stroke. Group 1 had damage to the left putamen but spared other left hemisphere regions that have previously been associated with speech production difficulties (parts of the ventral premotor cortex, the inferior longitudinal fasciculus and the temporo-parietal junction). Group 2 did not have damage to left putamen or other language regions but did have left hemisphere lesions matched in size to those in Group 1.

Results, so far: All patients with left putamen damage reported speech production difficulties in the month after their stroke which resolved, almost completely within the first year.

Conclusion: On completion, this study will contribute to our understanding of the putamen

S1-P28

Category: Cognitive & Behavioural Neuroscience

Overlapping frontoparietal network for tactile and visual working memory representations

Wu Y-h[1,2,*], Uluc I[1,2,*], Tertel K[1,2], Schmidt TT[2,3], Blankenburg F[1,2]

Affiliation: [1]Berlin School of Mind and Brain, Humboldt Universität zu Berlin
[2]Neurocomputation and Neuroimaging Unit, Freie Universität Berlin
[3]Institute for Cognitive Science, University of Osnabruck
[*]Equal contribution

Background: Neurophysiology and EEG studies on working memory (WM) have shown that frontal neurons parametrically encode stimulus frequencies across different sensory modalities (Spitzer & Blankenburg, 2012; Vergara et al., 2016). Such modality-independent WM representations indicate that stimulus frequencies are maintained in an abstract, quantitative, rather than in a sensory format. In human fMRI studies, stimulus-frequency-specific activity patterns during tactile WM have been observed in frontal regions using multivariate pattern analysis (MVPA; Schmidt et al., subm.). However, it is unclear to which extent these memory representations in human frontal regions can be generalized to other modalities.

Aims: We used fMRI-MVPA to test whether human frontal regions encode stimulus-frequency held in WM across different sensory modalities.

Methods: We acquired fMRI data while participants performed a cross-modal frequency discrimination task with tactile and visual stimuli. Searchlight-based MVPA was conducted to identify brain regions carrying information about stimulus-frequencies of both modalities. Moreover, we tested whether information from different modalities is represented in a similar way.

Results: Overlapping, modality-specific WM representations of tactile and visual frequencies were found in pre-SMA, right IFG, precuneus and IPS. Conversely, sensory areas only encode information from their corresponding modalities.

Conclusion: Our results suggest that frontal and parietal regions represent information at a higher level of abstraction. Future work should focus on dissociating these regions' functional contributions to mnemonic representation of abstract information.

S1-P29

Category: Cognitive & behavioural neuroscience

Tourette's Syndrome: The role of attention and inhibitory mechanisms in the generation and management of tics

Leanne N. Hockey[1], Patrick Haggard[2], John Rothwell[1] & Eileen M. Joyce[1]

Affiliations: [1]Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, UCL. [2]Institute of Cognitive Neuroscience, UCL, London, UK

Background: Tourette's syndrome (TS) is characterised by involuntary movements and vocalisations known as tics. Tics arise in childhood and overtime, severity often decreases. However, in a significant proportion, tics persist into adulthood and are socially disabling. Tics are thought to arise from a neurophysiological imbalance in the sensorimotor system. They are preceded by an 'urge' to tic and at this stage, some can actively suppress the tic from developing. Current psychological therapy uses this phenomenon to help people control their tics based on the hypothesis there is a problem with motor inhibition. However, this is often not successful in adults. Tics often automatically reduce when distracted or concentrating on something. This suggests that there may also be an additional problem with attention. Rather than focusing on urges to help prevent tics, learning distraction techniques may be a promising alternative therapy.

Aims: We propose to investigate the extent to which adult TS is associated with problems in attention and inhibition.

Methods: To do this we will: a) assess attention and inhibition on a range of cognitive tasks (novel CPT, RCF, CANTAB); b) assess neurophysiological imbalance using transcranial magnetic stimulation (TMS); and c) assess the relevance of comorbid symptoms to indices of impairment.

Results: Data collection underway.

Conclusion: Results may provide the basis for the development of new therapies.

S1-P30

Category: Imaging

Detecting focal cortical dysplasia in cryptogenic focal epilepsy

Samira Kashefi [1], Sophie Adler[5], Konrad Wagsty [5], Oscar Bennett[2], Sebastien Ourselin [2] and Gavin Winston[3, 4]

Affiliations:
[1] UCL Institute of Neurology
[2] Translational Imaging Group, Centre for Medical Image Computing, UCL, London, UK
[3] Departments of Clinical and Experimental Epilepsy, UCL Institute of Neurology, London, UK
[4] Epilepsy Society MRI Unit, Chalfont St Peter, UK
[5] Developmental Neurosciences, UCL Great Ormond Street Institute of Child Health, London, UK

Background: Focal epilepsy is characterized by localized minor structural changes of cerebral cortex and one third of adult patients do not respond to medication. Brain surgical resection can be the next best option if the abnormal brain region can be identified accurately on the MRI scans. However 30% of the patients have normal appearing MRI images ('MRI-negative'), making surgical planning difficult and expensive.

Aim: The purpose of this study to combine novel MRI surface-based approach called "doughnut method" with machine learning, which has shown to be effective in paediatric cohort (Adler et al 2017), and apply it in the adult population.

Methods: A retrospective cohort of 22 patients with histologically confirmed FCD (15 MR Positive, 7 MR negative) with 3T MRI (T1, FLAIR) images were selected. Freesurfer was used for cortical and subcortical segmentations. A 6mm radius circle was centred on each vertex on the inflated brain-surface. The cortical deformation and abnormal grey-white matter intensity contrast within the circle and within the doughnut was measured. Neural-network classifiers will be trained to classify vertices as lesional or healthy cortex. Clusters below 200 vertices will be excluded as noise and above will be considered putative lesion.

Result: We predict that this approach will identify the epileptogenic region in a proportion of MRI-negative patients.

Conclusion: If this novel automated method proven to be more sensitive in detection of epileptic zones in adult then it may be considered alongside other noninvasive approaches to enable earlier and more effective assessment for surgical intervention.

S2: Session 2 (10:35-11:25)

S2-P01

Category: Molecular Neuroscience

Role of Synaptotagmin 1 ring-like oligomers in regulating endocytosis at central synapses

Langley H[1], Tagliatti E[1], Bello O[1], Krishnakumar SS[1,2], Rothman JE[1,2], Volynski KE[1]

Affiliations: [1]UCL Institute of Neurology, University College London London, UK
[2]Department of Cell Biology, Yale University School of Medicine, New Haven, Connecticut, USA

Background: Fast synchronous neurotransmitter release from synaptic nerve terminals involves tightly-regulated presynaptic machinery. The major calcium sensor and trigger for fast evoked release is synaptotagmin (Syt1/2/9 in different neurons). Recently, it has been demonstrated that Syt molecules readily form Ca^{2+}-sensitive ring-like oligomers on lipid surfaces (Wang et al. 2015 and Zanetti et al 2016). Several lines of evidence indicate that these structures may be physiologically relevant for synaptic vesicle exo- and endocytosis.

Aims: We test the role of Syt1 rings in regulating synaptic vesicle endocytosis in small central synapses in culture. We investigate the effect of a Syt1 point mutation (F349A), which disrupts formation of Syt1 rings in vitro, on clathrin-dependent and clathrin-independent mechanisms of endocytosis.

Methods: We overexpress a Syt1 F349A construct fused to the vesicular release sensor pHluorin and examine endocytosis kinetics using fluorescence microscopy in primary neocortical neuronal cultures from mice.

Results: Syt1 F349A-pHluorin increases the rate of synaptic vesicle retrieval when compared to wild type control. The effects of F349A differ depending on stimulus frequency (5Hz vs 40Hz trains).

Conclusion: Syt1 ring formation is involved in synaptic vesicle endocytosis, but this involvement appears to differ between clathrin-dependent and clathrin-independent endocytosis mechanisms

S2-P02

Category: Molecular Neuroscience

Validation of a method for detection of low-level single nucleotide variant mosaicism in sporadic Parkinson's disease

M. I. Leija Salazar[1], K. Mokretar[1], A. Pittman[2], D. Hughes[2], M. Athanasopoulou[2], H. Morris[1], A. Schapira[1], C. Proukakis[1]

Affiliations: [1]Dept of Clinical Neurosciences, Institute of Neurology, University College London, London, United Kingdom, [2]Dept of Molecular Neuroscience, Institute of Neurology, University College London, London, United Kingdom

Background: Although the pathological role of somatic mutations remains undetermined, the mechanisms of neurodegeneration could be explained by their occurrence in brain.

Aims: To optimise a robust sequencing method for sensitive detection of somatic variation in sporadic Parkinson's Disease (PD) samples.

Methods: Sequencing libraries were prepared by using a Haloplex HS panel (Agilent) targeting *SNCA, GBA* and coding exons of 12 PD genes. Six artificial mosaics, which consist of low dilutions of a brain sample carrying known variants, were sequenced on a HiSeq 2500. Sequencing data processing was done by Surecall, which takes advantage of molecular barcodes to remove duplicates and generate consensus sequences that replicate original DNA fragments. LoFreq was used as an independent variant caller for validation of Surecall's results. Criteria for false positive filtering were established by variant validation on IGV

Results: At 2050x coverage, four false positives were detected at allele frequencies below 0.33%. Known variant analysis in artificial mosaics showed a sensitivity of 92% using Surecall and LoFreq to detect 1% variants, whereas at 0.5% LoFreq and Surecall showed sensitivities of 84% and 78%, respectively.

Conclusion: Deep sequencing of PD samples using Haloplex HS allows for sensitive detection of variants at >0.33% allele frequency. These methods will be used for the analysis of 50 samples from different brain regions and other tissues.

S2-P03

Category: Molecular neuroscience

Title: Genetic and proteomic profiling of sporadic, familial and TREM2 variant Alzheimer's disease post-mortem brains

Murray C.E.[1], Gami-Patel P.[1], Kiely A.P.[1], Holton J[1], Heywood W.E.[2], Mills K.[2], Lashley T.[1]

Affiliations: [1]Queen Square Brain Bank for Neurological disorders, UCL Institute of Neurology, London, United Kingdom; [2]Centre for Translational Omics, Institute of Child Health, UCL, London, United Kingdom

Background: The underlying pathogenesis of Alzheimer's disease (AD) remains elusive. Recent observations indicate that neuroinflammation may play a role in the causative mechanism.

Aim: To explore gene expression of inflammatory/AD-related genes and the proteomic profile in post-mortem brains from AD cases.

Methods: RNA was extracted from the frontal cortex of sporadic AD (n=10), familial AD (n=7), *TREM2* variant cases (n=6) and normal controls (n=6). Samples were analysed using the Nanostring human inflammation panel (256 genes) and 30 genes implicated in AD. Proteins were extracted and analysed using label-free mass spectrometry with a SYNAPT G2-Si High Definition machine with 2D fractionation.

Results: Compared to controls, 126 genes had statistically different expression levels ($p<0.05$) in sporadic AD, 93 genes in familial AD, and 57 in *TREM2* variant cases. A total of 8313 proteins were identified using mass spectrometry. Compared to controls, 188 proteins had greater than 2 fold change expression levels in sporadic AD, 410 in familial AD, and 346 in *TREM2* variant cases. Greater variation of up- and down- regulation was seen at the protein level compared to being predominantly up regulated at the gene level.

Conclusions: Inflammatory gene expression differs between AD subgroups indicating the two disease groups may not share a common pathway. Alterations in the protein expression of some of these genes however suggest that there could be compensatory mechanisms occurring at the translational level.

S2-P04

Category: Molecular neuroscience

Gene therapy for epilepsy using non-integrating lentiviral delivery of an engineered potassium channel gene

A. Snowball, E. Chabrol, B-L. Chang, A. Lieb, M. C. Walker, D. M. Kullmann, S. Schorge

Gene therapy is a promising treatment strategy for pharmacoresistant epilepsy. While several approaches have demonstrated preclinical efficacy, their suitability for clinical translation can be brought into question by poor vector or study design. Here we present a novel gene therapy vector designed and tested to maximise its translational potential. The vector encodes a Kv1.1 voltage-gated potassium channel gene, *KCNA1*, engineered to increase channel expression and reduce inactivation. To improve safety, the engineered *KCNA1* sequence is placed under a CAMK2A promoter to restrict transgene expression to excitatory neurons, and packaged into an integration-deficient lentivirus to reduce the risk of insertional mutagenesis. When injected into the rat visual cortex, our lentivector was well tolerated and drove transgene expression specifically within the target excitatory neuron population. In a randomised, blinded, preclinical trial (performed with adherence to ARRIVE guidelines), our treatment rapidly and persistently suppressed seizures in a rodent model of focal neocortical epilepsy. This demonstration of therapeutic efficacy in a clinically-relevant setting, combined with the improved safety conferred by cell type specific expression and integration-deficient delivery, suggest our optimised gene therapy is well placed for clinical translation in the treatment of refractory focal epilepsy.

S2-P05

Category: Molecular Neuroscience

Huntington's disease blood and brain show a common gene expression pattern and share an immune signature with Alzheimer's disease

Michael D. Flower[1], Davina J. Hensman Moss[1], , Kitty K. Lo[2], James R. C. Miller[1], Gert-Jan B. van Ommen[3], Peter A. C. 't Hoen[3], Timothy C. Stone[4], Amelia Guinee[5], Douglas R. Langbehn[6], Lesley Jones[4], Vincent Plagnol[2], Willeke M. C. van Roon-Mom[3], Peter Holmans[4], & Sarah J. Tabrizi[1]

Affiliations: [1]Department of Neurodegenerative Disease, University College London Institute of Neurology, London, WC1B 5EH, UK
[2]University College London Genetics Institute, University College London, London, WC1E 6BT, UK
[3]Department of Human Genetics, Leiden University Medical Center, Leiden, Postzone S-4-P, The Netherlands
[4]MRC Centre for Neuropsychiatric Genetics and Genomics, School of Medicine, Cardiff University, CF24 4HQ, UK
[5]Faculty of Education, University of Cambridge, CB2 8PQ, Cambridge UK
[6]Departments of Psychiatry and Biostatistics, University of Iowa, IA 52242, USA

Background: There is widespread transcriptional dysregulation in Huntington's disease (HD) brain, but analysis is inevitably limited by advanced disease and postmortem changes. However, mutant *HTT* is ubiquitously expressed and acts systemically, meaning blood, which is readily available and contains cells that are dysfunctional in HD, could act as a surrogate for brain tissue.

Aims: Measure and analyse the changes in gene expression in whole blood of Huntington's disease patients and controls.

Methods: We conducted an RNA-Seq transcriptomic analysis using whole blood from two HD cohorts, and performed gene set enrichment analysis using public databases and weighted correlation network analysis modules from HD and control brain datasets.

Results: We identified dysregulated gene sets in blood that replicated in the independent cohorts, correlated with disease severity, corresponded to the most significantly dysregulated modules in the HD caudate, the most prominently affected brain region, and significantly overlapped with the transcriptional signature of HD myeloid cells. High-throughput sequencing technologies and use of gene sets likely surmounted the limitations of previously inconsistent HD blood expression studies.

Conclusion: Our results suggest transcription is disrupted in peripheral cells in HD through mechanisms that parallel those in brain. Immune upregulation in HD overlapped with Alzheimer's disease, suggesting a common pathogenic mechanism involving macrophage phagocytosis and microglial synaptic pruning, and raises the potential for shared therapeutic approaches.

S2-P06

Category: Molecular Neuroscience

Design and optimisation of an in vitro model of the corticostriatal pathway using iPSC-derived neurons to investigate loss of connectivity in Huntington's disease

Caroline S Casey[1,2], Matthew P Bentham[1,3], Giampietro Schiavo[3], Selina Wray[4], Ralph Andre[1,2], Alison Wood-Kaczmar[1,2], Sarah J Tabrizi[1,2]

Affiliations: [1]IoN, University College London; [2] Huntington's Disease Centre, University College London; [3] Sobell Department of Motor Neuroscience and Movement Disorders, IoN University College London; [4] Department of Molecular Neuroscience, IoN University College London

Background: The corticostriatal (CS) pathway has been shown to be disrupted in Huntington's disease (HD) and is thought to underlie the movement disorder experienced by HD patients throughout disease progression. The CS pathway is composed of glutamatergic cortical neurons, which project and synapse onto medium spiny neurons (MSN) in the striatum. MSNs account for 90-95% of neurons in the striatum and are considered the most vulnerable to pathology in HD. Indeed, the striatum is the primary area of neurodegeneration in the disease. Until now, cell models of this pathway have been limited to either rodent or mixed species co-cultures. However, with the advances in induced-pluripotent stem cell (iPSC) technology, we are now able to consistently generate human cortical neurons and MSNs that are stereotypical of those in the brain.

Aims: The aim of this work is to design and optimise a platform in which iPSC-derived cortical neurons and MSNs can be co-cultured, to replicate the CS pathway in both control and HD patient derived cells.

Methods and Results: Here we show that cortical neurons can successfully project and begin to form networks in microfluidic chambers. By using sequential plating methods, we are able to introduce MSNs to the axon terminals of cortical neurons in isolation from the somal compartment. This encourages synapse formation and function representative of neurological development.

Conclusion: Our modelling of the CS pathway in human cells enables the direct comparison of healthy and HD brain circuitry in an *in vitro* format.

S2-P07

Category: Molecular Neuroscience

Mutations in NKX6-2 cause progressive spastic-ataxia and hypomyelination

Viorica Chelban[1,7], Nisha Patel[2], Jana Vandrovcova[1], Natalia Zanetti[3], David S Lynch[1], Mina Ryten[9,10], Juan A Botía[9,11], Oscar Bello[3], Eloise Tribollet[1], Stephanie Eftymiou[1], SYNaPS study group, Indran Davagnanam[8], Fahad Bashiri[6], Nicholas Wood[1,4], Fowzan S Alkuraya[2,5] and Henry Houlden[1,4]

Affiliations: [1]Department of Molecular Neuroscience, [3]Department of Clinical and Experimental Epilepsy, [8]Department of Brain Repair & Rehabilitation, [9]Reta Lila Weston Research Laboratories, Institute of Neurology, University College London, London WC1N 3BG, UK.
[2]Developmental Genetics Unit, Department of Genetics, King Faisal Specialist Hospital and Research Center, MBC 03, PO Box 3354, Riyadh 11211 Saudi Arabia.
[4]Neurogenetics Laboratory, The National Hospital for Neurology and Neurosurgery, London WC1N 3BG, UK.
[5]Department of Anatomy and Cell Biology, College of Medicine, Alfaisal University, Riyadh 11533, Saudi Arabia
[6]Department of Pediatrics, College of Medicine, King Saud University, Riyadh 11451, Saudi Arabia
[7]Department of Neurology and Neurosurgery, Institute of Emergency Medicine, Chisinau, Republic of Moldova.
[10]Department of Information and Communications Engineering, University of Murcia, Spain
[11]Department of Medical & Molecular Genetics, King's College London, Guy's Hospital, London, UK

Background: The combination of progressive limb spasticity and cerebellar ataxia are frequently found in clinical practice and form a heterogeneous group of degenerative disorders that are classified as either pure spastic ataxia, or complex with additional neurological signs. Inheritance is either autosomal dominant or recessive. Hypomyelinating features on MRI are not uncommonly seen with spastic-ataxia but this is usually mild in adults, and severe and life-limiting in children.
Aim: To describe for the first time a human phenotype associated with mutations in the *NKX6-2* gene in seven individuals from three families of different ethnic background with an early-onset spastic-ataxia phenotype.

Methods: Using a combination of homozygozity mapping and exome sequencing we mapped this phenotype to deleterious non-sense or homeobox domain missense mutations in the *NKX6-2* gene.

Results: Two families had childhood onset disease with very slow progression, and are still alive in their 30s/40s with predominant ataxia and cerebellar atrophy features on imaging. The third family had a similar but very early-onset presentation associated with brain hypomyelination. *NKX6-2* is a transcriptional repressor with early high general and late focused CNS expression. Deficiency of its mouse ortholog results in widespread hypomyelination in the brain and optic nerve, and poor motor coordination in a pattern consistent with the observed human phenotype.

Conclusion: Our results support a non-redundant developmental role of *NKX6-2* in humans and imply that *NKX6-2* mutations should be considered in the differential diagnosis of spastic-ataxia and hypomyelination.

S2-P08

Category: Molecular Neuroscience

Identification of genetic variants associated with Huntington's disease progression

Davina J Hensman Moss*[1], Antonio F. Pardiñas*[2], Douglas Langbehn[3], Kitty Lo[4], Blair R. Leavitt[5], Raymund Roos[6], Alexandra Durr[7], Simon Mead[8], Peter Holmans[2], Lesley Jones[§2], Sarah J Tabrizi[§1] and the REGISTRY and the TRACK-HD investigators.

Affiliations: [1]UCL Huntington's Disease Centre, UCL Institute of Neurology, Dept. of Neurodegenerative Disease, London, UK
[2] MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, UK
[3] University of Iowa Carver College of Medicine, Dept. of Psychiatry and Biostatistics, Iowa, USA
[4]UCL Genetics Institute, Div. of Biosciences, London, UK
[5] Centre for Molecular Medicine and Therapeutics, Department of Medical Genetics, University of British Columbia, Vancouver, British Columbia, Canada
[6]Department of Neurology, Leiden University Medical Centre, Leiden, Netherlands
[7]ICM and APHP Department of Genetics, Inserm U 1127, CNRS UMR 7225, Sorbonne Universités, UPMC Univ Paris 06 UMR S 1127, Pitié- Salpêtrière University Hospital, Paris, France
[8]MRC Prion Unit, UCL Institute of Neurology, London, UK

Background: Age at onset (AAO) and progression in Huntington's disease (HD) are variable; genetic variation other than CAG modifies them.

Aim: Identify genetic modifiers of HD using a novel measure of disease progression.

Methods: We generated a progression score based on principal component analysis of longitudinal changes in the TRACK-HD cohort; 216 subjects were genotyped. We generated a parallel progression score using 1773 previously genotyped subjects from the REGISTRY study. Genetic analysis was performed using GCTA, MAGMA, METAL.

Results: Longitudinal motor, cognitive and imaging scores were correlated in TRACK-HD. TRACK-HD and REGISTRY progression measures were correlated with each other (r=0·674), and AAO (r=0·315, r=0.234 respectively). A meta-analysis of progression in TRACK-HD and REGISTRY gave a genome-wide significant signal ($p=1.12x10^{-10}$) on ch5. The association region spans 3 genes, each significantly associated with progression in both TRACK-HD and REGISTRY. The lead SNP in TRACK-HD (rs557874766) is genome-wide significant in the meta-analysis ($p=1.58x10^{-8}$), and encodes a protein change in MSH3. Each copy of the minor allele is associated with a 0.1 units/year change in rate UHDRS Total Functional Capacity change. Associations remained significant after adjusting for AAO.

Conclusion: A locus on ch5 is associated with progression in HD. Observing such a strong association in 216 subjects implies our progression measure is sensitive, the effect size is large, or both. The variant is a coding change in *MSH3* and knock out of MSH3 reduces somatic expansion in HD mouse models, highlighting somatic expansion as a potential pathogenic modulator in HD patient, informing therapeutic development.

S2-P09

Category: Molecular Neuroscience

Idh1 mutation predispose glioma initiating cells to apoptosis under endoplasmic reticulum (ER) stress

Ying Zhang[1], Ningning Li[1], Joanne Lau[1], Angela Richard-Londt[1], Stefan Pusch[2], Andreas von Deimling[2], and Sebastian Brandner[1]

Affiliations: [1]Department of Neurodegeneration, UCL Institute of Neurology
[2]Department of Neuropathology, Institute for Pathology, University of Heidelberg, Germany

Background: IDH mutations are frequent genetic alterations in gliomas in young and middle-aged adults. Patients with IDH mutant gliomas survive significantly longer than those with IDH wild type (wt) gliomas.

Aims: To investigate how Idh mutation confers a better prognosis compared with Idh wt gliomas.

Materials/Methods: Stem/progenitor cells derived from murine subventricular zone were recombined with Cre recombinase in vitro resulting $Idh1^{R132H}/p53^{-/-}/Pten^{-/-}$ or $p53^{-/-}/Pten^{-/-}$ glioma initiating cells (GICs). RNA and microRNA sequencing were performed on the two types of GICs. Intrinsic gliomas were generated by transducing stem cells with retrovirus co-expressing PDGFB and Cre.

Results: Idh1 mutation significantly inhibited proliferation, but promoted apoptosis in vivo and in vitro. Gene Set enrichment analysis showed a significant enrichment of genes involved in ER stress related apoptosis in Idh1 mutant GICs. Treatment of GICs with tunicamycin and tharpsigargin, two ER stress inducers, caused significant apoptosis in Idh1 mutant cells but not in wt cells. However, the increase of apoptosis was similar in mutant and wt cells when treated with H_2O_2, chloroquine, MG-132 and under hypoxic conditions. Analysing miRNA profiles identified the upregulation of miR-27 and miR-183 cluster in Idh1 mutant GICs. The two microRNA clusters have been reported to promote cell death during ER stress response.

Conclusion: Idh1 mutant GICs were predisposed to apoptosis under ER stress, which could be mediated by upregulation of miR-27 and miR-183 family.

S2-P10

Category: Molecular Neuroscience

Distinct Aβ production in stem cell-derived cortical neurons from patients with fAD mutations

Jamie Toombs[1], Charles Arber[1], Natalie Ryan[2], Amanda Heslegrave[1], John Hardy[1], Nick Fox[1], Selina Wray[1], Henrik Zetterberg[1,3]

Affiliations: [1]Department of Molecular Neuroscience, UCL Institute of Neurology. [2]Department of Neurodegeneration, Institute of Neurology, Dementia Research Centre, London, UK. [3]Department of Psychiatry and Neurochemistry, Institute ofNeuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden

Background: Mutations in the *APP* and *PSEN1* genes can alter amyloid beta (Aβ) peptide production and lead to inherited forms of Alzheimer's disease (fAD). Characterisation of the consequences of these mutations in humans is still limited.

Aims: To investigate production of Aβ and total tau (T-tau) in the media of cultured human fAD neurons.

Methods: Cortical neurons were induced from three non-neurodegenerative controls (two iPSC and one hESC), and three fAD (APP V717I, *PSEN1* intron 4 deletion, and *PSEN1* M139V) induced pluripotent stem cell (iPSC) lines. Media was collected from three inductions of each line at days 100 and 200 post-induction and assayed for Aβ38/40/42 and T-tau using a Meso Scale Discovery SECTOR 6000.

Results: All following results are presented as the average of day 100 and 200 ± standard error. All control lines secreted Aβ in similar ratios (Aβ42:40 = 0.1±<0.1, Aβ42:38 = 0.4±<0.1, Aβ40:38 = 4.0±<0.1). Versus controls, *APP* cells demonstrated increased Aβ42:40 (0.2±<0.1), slightly increased Aβ42:38 (0.5±<0.1), and decreased Aβ40:38 (2.5±<0.1). *PSEN1* intron 4 deletion cells had increased Aβ42:40 (0.2±<0.1), increased Aβ42:38 (1.2±<0.1) and increased Aβ40:38 (5.3±<0.1). *PSEN1* M139V cells had increased Aβ42:40 (0.2±<0.1), increased Aβ42:38 (0.9±<0.1), and slightly increased Aβ40:38 (4.4±<0.1). Aβ:T-tau ratios were highly variable (23.8%CV±<1.8) and yielded little distinction between cell lines.

Conclusion: Human cortical neurons harbouring specific fAD mutations all increased Aβ42:40 secretion into the extracellular space (by approximately two-fold) versus controls. The Aβ40:38 ratio distinguished well between different mutations. Results shed light on γ-secretase cleavage pathways for the generation of Aβ.

S2-P11

Category: Molecular neuroscience

Development of an in vitro assay of prion-induced toxicity

Reilly M, Benilova I, Jat P, Collinge J

Affiliations: Department of Neurodegenerative Disease and MRC Prion Unit, UCL Institute of Neurology.

Background: Prion propagation proceeds through an asymptomatic exponential phase in which infectivity rapidly reaches peak titre, independent on the expression level of PrP^{C}. This is followed by a plateau continuing until clinical onset, with a length inversely proportional to the expression level of PrP^{C}. Neuropathology in prion disease is detected only after prion titre saturates and this is coupled to a linear rise in disease-associated PrP isoforms, that do not meet the classical definition of PrP^{Sc}. It is proposed neuropathology relates to a subset of these isoforms, deemed PrP-lethal (PrP^{L}) produced in direct proportion to PrP^{C} after prion titre saturates.

Aims: To identify, characterise and elucidate the mechanism of action of PrP^{L}, a robust *in vitro* assay of neurotoxic activity must be developed. The assay will need to quantitatively measure neuronal dysfunction upon exposure to prion-infected material and have a dynamic range sufficient to detect toxicity from brain homogenates of mice at different stages of clinical disease.

Methods: Quantification of RML prion–infected brain homogenate toxicity in primary neuronal cultures by the analysis of images taken by fluorescence microscopy.

Results: RML-prion infected brain homogenate toxicity is quantifiable through image analysis. Read-outs include neuronal loss, neurite fragmentation, dendritic spine atrophy and gliosis.

Conclusion: Utilising high content microscopy and image analysis, brain homogenates taken from mice at different stages of prion infection will be assayed for prion–induced neurotoxicity

S2-P12

Category: Molecular Neuroscience

In vitro modelling of mitochondrial disease using human induced pluripotent stem cell derived myotubes harbouring mtDNA mutations.

Ben O'Callaghan[1], Monika Madej[1], Michael G. Hanna[1], Jennifer Morgan[2], Henry Houlden[1]

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

Background: Mitochondrial diseases are a heterogeneous group of disorders caused by genetic dysfunction of mitochondrial oxidative phosphorylation (OXPHOS). Patients present with a range of clinical symptoms which generally affect tissues with high cellular energy requirements such as muscle.

Aims: We are investigating the effect that mtDNA mutations causing Myoclonic Epilepsy with Ragged Red Fibre (MERRF) syndrome and Mitochondrial Encephalopathy Lactic Acidosis (MELAS) syndrome 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 have been reprogrammed using non-integrating delivery methods. Human induced pluripotent stem cell (hIPSC) lines are being differentiated into myotubes using defined factors which recapitulate the developmental stages of myogenesis. Live cell imaging will be used to assess mitochondrial function and metabolism in differentiated myotubes.

Results: Isogenic hIPSCs with differing heteroplasmy levels have been established from a MELAS m.3243A>G and three unrelated MERRF m.8344A>G patients. hIPSCs with/without mtDNA mutations have been successfully differentiated into $MyHC^{+}/Titin^{+}/Myogenin^{+}$ myotubes which retain a non-proliferative $PAX7^{+}/Ki67^{-}$ satellite-like cell niche. Preliminary results of mitochondrial function will also be presented.

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

S2-P13

Category: Molecular neuroscience

An induced pluripotent stem cell model of Hereditary Spastic Paraplegia

Luke Hill PhD Student

Affiliations: Department of Molecular Neuroscience

Primary Supervisors: Professor Tom Warner, Professor Rickie Patani

Background: Hereditary spastic paraplegias are a heterogeneous group of hereditary neurological movement disorders. They are the second most common cause of motor neuron disease behind amyotrophic lateral sclerosis. Over seventy genetic sub-types of hereditary spastic paraplegia have been described (Spastic gait loci SPG1-77). Patients typically present with lower limb weakness and spasticity due to degeneration of upper motor neurons of the corticospinal tract. However, in certain genetic subtypes patients can also present with other complicating neurological symptoms due to wider spread degeneration of the nervous system. *SPG11* and *SPG15* are the two most common types of autosomal recessive hereditary spastic paraplegia. Patients present with similar phenotypes including lower limb weakness and spasticity as well as cognitive impairment, ataxia, peripheral neuropathy, retinal abnormalities and thinning of the corpus callosum. The two protein products of *SPG11* (spatacsin) and *SPG15* (spastizin) are binding partners in the cell. Moreover, most knockout disease phenotypes across SPG11 and SPG15 models are phenocopies, suggestive that spatacsin and spastizin function in the same cellular pathway.

Aims: To investigate the cellular and molecular pathogenesis of *SPG11* and *SPG15* using a variety of disease relevant patient induced pluripotent stem cell derived neuronal subtypes.

Results / conclusion: Induced pluripotent stem cell lines have been generated from three independent *SPG11* patients, two independent *SPG15* patients and six control subjects. This model will now be used to investigate the cellular and molecular pathogenesis of *SPG11* and *SPG15*.

S2-P14

Category: Molecular Neuroscience

Direct differentiation of human cell lines to neuronal cell fate

Flora C.Y. Lee[1,2], Katia B. Egli[1,2], Jernej Ule[1,2]

Affiliations: [1]Department of Molecular Neuroscience, UCL Institute of Neurology
[2]Francis Crick Institute

Background: Studies with human neurons in cell culture help to better understand human physiology and pathology, complementary to work done in other model organisms. Human induced pluripotent stem cell (hiPSC)-derived neurons are currently the gold standard for generating human neurons *in vitro*. However, reprogramming and maintenance of hiPSCs is laborious. Direct conversion of immortalised somatic cells into neurons may present an alternative model.

Aims: To investigate the capacity and efficiency of neuronal transdifferentiation on human immortalised fibroblasts (BJ-5ta), HEK293 and HAP1 cell lines.

Methods: Cells inducibly expressing Brn2 are transduced with lentivirus to knockdown *PTBP1* (polypyrimidine tract-binding protein 1). Subsequently, a cocktail of small molecules and growth factors is used to drive neuronal differentiation and maturation.

Results: BJ-5ta display morphological changes upon PTBP1 knockdown and/or Brn2 expression. In contrast, PTBP1 knockdown alone was unable to induce neuronal transdifferentiation from HEK293 cells. Neuronal markers are characterized by immunocytochemistry and RT-PCR.

Conclusion: We are considering direct neuronal conversion from immortalized fibroblasts as an alternative to the generation of hiPSC-derived neurons. Further work is required to fully assess the conversion efficiency and degree of neuronal maturation. We are actively exploring the neuronal transdifferentiation capacity of our existing HEK293 and HAP1 cell lines, respectively, to take advantage of stably inserted expression cassettes for proteins of interest, or the relative ease of genome-editing in a haploid genome.

S2-P15

Category: Molecular Neuroscience

Response of Satellite glia cells in the dorsal root ganglion to inflammatory stimuli in vitro

Yadav A, Alqatari M[1], Koltzenburg M[1]

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

Background: The dorsal root ganglion (DRG) is a well-established part of the pain pathway.The majority of pain research concentrates on DRG neurons, however increasingly focus has shifted to the resident glial cells here. These satellite glial cells (SGCs) tightly wrap sensory neurons but little is known about their function. It has been suggested that they have a role in modulating the properties of sensory neurons and that Toll-like receptor 4 (TLR4) are also involved.

Aims: To investigate whether Lipopolysaccharide (LPS), an agonist of TLR4 regulates the expression of biomarkers of SGCs for example, glial fibrillary acid protein (GFAP) *in vitro*. To investigate how the expression of markers of SGCs changes over time in culture.

Methods: Cell cultures are prepared from neonatal rat pup DRG and maintained for 2, 24, 96 and 144 hours. Culture will be stained with markers for SGCs e.g. GFAP. LPS (5µg/ml) will be used to stimulate SGCs. Fluorescent microscopy will be used to image the cells.

Results: In both control and LPS-stimulated cultures, GFAP is seen to be upregulated from 24 hours onwards. It is hypothesized that LPS will cause an effect such as an upregulation in the glial markers.

Conclusion: The expression of biomarkers of SGCs such as GFAP are changing over time in culture. We will determine whether activation of the TLR4 pathway alters this expression pattern.

S2-P16

Category: Molecular Neuroscience

Mapping interactions of genetic loci associated with Parkinson's disease using in situ DNase Hi-C

Storm C[1], Kia D[1], Pittman A[1], Manzoni C[1], Wood N[1]

Affiliations: Department of Molecular Neuroscience, UCL Institute of Neurology

Background: Genome-wide association studies (GWAS) have identified common genetic variants, single nucleotide polymorphisms (SNPs), that modify an individual's risk of developing Parkinson's Disease (PD). It has been hypothesised that SNPs affect disease risk by altering gene expression. The three-dimensional organisation of DNA contributes to gene regulation, which can be studied using Hi-C, a genome-wide chromosome conformation capture technology that ascertains physical contacts between genomic regions.

Aims: To assess whether genomic regions containing PD-associated variants participate in physical chromatin interactions.

Methods: DNA-to-DNA interactions were identified in the human neuroglioma cell line H4 using *in situ* DNase Hi-C, a newly developed 3C technology. Statistically confident interactions were ascertained using publically available Hi-C packages. An in-house pipeline was used to assess whether PD risk loci, defined using most recent GWAS data, participate in long-range chromatin interactions.

Results: At 1 Mb resolution, five PD-associated loci were found to participate in statistically confident long-range chromatin interactions. One sequence containing PD-associated SNPs near *HLA-DQB1* appears to contact a region containing *PARK2*, where mutations can cause monogenic PD.

Conclusion: These results show promise in exploring whether GWAS-identified loci mediate their effect on PD risk via spatial elements of gene regulation. The method is currently being refined to improve the resolution and model.

S2-P17

Category: Molecular neuroscience

Sequencing screening and validation of mutations in frontotemporal dementia

Anila Minhas, Dr Raffaele Ferrari[1]

Affiliations: [1] Department of Molecular Neuroscience, UCL Institute of Neurology.

Background: Frontotemporal dementia (FTD) is the second most common form of young-onset dementia after Alzheimer's disease. It accounts for 10-20% of all dementias worldwide. The prevalence of FTD is 3-15 per 100 000 individuals: age at onset ranges between 55 and 65 years. The disease has a gradual onset: in 30-50% of patients it is familial and equally affects men and women.
Three genes (*MAPT*, *GRN* and *C9orf72*) explain 7-20% of all cases, whilst a handful of other genes (*TDP-43, CHMP2B, VCP, FUS, SQSTM1, UBQLN2, IFT74, OPTN, DCTN1 and CHCHD10)* accounts for less than 5% of all cases.

Aims: To validate coding risk variants associated with FTD and expand on the genetic landscape of rare variability in frontotemporal dementia.

Methods: Data generated through the Neuro-X genotyping exome chip indicated a number of rare coding variants in known and novel potential genes associated with FTD. Provided data is analyzed at the genotyping level, any variant needs to be replicated and validated through a different method including Sanger sequencing.

Results: We are sequencing 12 variants for 9 genes. This far our results indicate coding variants in known (*GRN, TREM2* and *VCP*) and novel potential (*NELL1, PANK2* and *ACE)* genes for FTD. For the remainder variants Sanger sequencing is ongoing.

Conclusion: Neuro-X genotyping exome chip allows to quickly screen large cohorts for mutations in neurodegenerative genes but also might highlight presence of pleiotrophy across neurodegenerative conditions.

S2-P18

Category: Molecular Neuroscience

Association between genetic risk variants and tau and α-synuclein neuropathology in Parkinson disease cases

Tchorek-Bentall M[1], Kia D[1], Nortley R[1], Ferrari R[1], Murray C[2], Lashley T[2], Pittman A[1], Holton J[2], Wood N[1]

Affiliations: [1]Department of Molecular Neuroscience, UCL Institute of Neurology, [2]Queen Square Brain Bank, UCL Institute of Neurology

Background: Parkinson disease (PD) is a neurodegenerative disorder characterised by progressive motor dysfunction including bradykinesia, resting tremor and postural instability. PD neuropathology is characterised by accumulation of misfolded α-synuclein in Lewy bodies and neurites in widespread brain regions. Neurofibrillary tau tangles also occur in PD. Genome-wide association studies have succeeded in identifying over 20 PD-associated risk loci, with polymorphisms associated with the *SNCA* and *MAPT* genes being most widely replicated.

Aims: In this study, we aimed to investigate the relationship between PD *SNCA* and *MAPT*-associated risk SNPs and α-synuclein and tau neuropathology load in patients diagnosed clinically with sporadic PD.

Methods: 54 cases were sequenced using the Sanger method or genotyped on an array. Case brain tissue pathology was stained with KM51 anti-α-synuclein antibody and AT8 anti-tau antibody in entorhinal, cingulate and temporal cortex. Pathology densitometry analysis was performed using ImageJ software. A linear regression interaction model was used to measure the interactive effect of SNP risk allele dose on PD neuropathology.

Results: Interactively, *SNCA* and *MAPT* risk alleles were found to significantly increase ($p<0.05$) total tau and α-synuclein pathology in PD brain tissue.

Conclusion: This study highlights the association of PD risk SNPs with disease pathology as well as risk of diagnosis, demonstrating the synergistic interaction of *SNCA*- and *MAPT*-associated SNPs in increasing PD pathology.

S2-P19

Category: Molecular Neuroscience

Identification of biological markers which differentiate satellite glia cells from Schwann cells in dorsal root ganglia

Lewin S[1], Alqatari M[1]

Affiliations: [1] Sobell Institute and Division of Neurophysiology, UCL Institute of Neurology

Background: Glial cells play an essential role in the nervous system. In the peripheral nervous system, satellite glial cells (SGCs) are less well characterised. Evidence suggests that they interact with primary afferent neurons, within dorsal root ganglia (DRG), via neurotrophic factors and may play an important role in inflammation and neuropathy.

Aims: To develop a culture system that allows identification of SGC and distinguishes it from other non-neuronal cells present in DRG, particularly Schwann cells.

Methods: Cultures of DRG were prepared from P0/P1 rats which contain both SGCs and Schwann cells. Fluorescent immunohistochemistry of the cultures is being carried out at different times in vitro, using a range of markers including S100β and Vimentin. These will be compared with pure SGC and Schwann cell cultures. Images will be captured and quantified using a fluorescent microscope and dedicated software.

Results: We hypothesize that the morphology and the markers S100β and Vimentin will allow us to distinguish between SGCs and Schwann cells in DRG cultures, and therefore allow us to characterise the function of SGCs in cell culture over time.

Conclusion: Further investigation could involve comparing results with other markers such as Glutamate Aspartate Transporter (GLAST) and Aquaporin 4, to define the optimum markers for characterising SGCs. The optimum markers could then be used to characterise the morphology of SGCs in neuropathic pain models.

S2-P20

Category: Molecular Neuroscience

Analysis of GAA repeat interruptions in a large panel of Friedreich ataxia patient DNA samples

Al-Mahdawi, S.[1,2]*, Ging, H.[3]*, Bayot, A.[3], Cavalcanti, F.[4], La Cognata, V.[5], Cavallaro, S.[5], Giunti, P.[3] and Pook, M.A.[1,2],*

*Affiliations: [1]Ataxia Research Group, Biosciences, Department of Life Sciences, CHLS, and [2]SBTheme, IEHS, Brunel University London, Uxbridge, UB8 3PH, UK; [3]Department of Molecular Neuroscience, UCL, Institute of Neurology, Queen Square, London, WC1N 3BG, UK; [4]Institute of Neurological Sciences, National Research Council, Contrada Burga, 87050 Mangone, Cosenza, Italy; [5]Institute of Neurological Sciences, National Research Council, Via Paolo Gaifami, 18, 95126, Catania, Italy. * = Joint first author.*

Background: Friedreich ataxia (FRDA) is a multi-system autosomal recessive inherited disorder primarily caused by homozygous GAA repeat expansion mutations within intron 1 of the frataxin (FXN) gene. The GAA repeat expansions may be pure (GAA)n in sequence or may be interrupted with regions of non-GAA sequence, such as (GAAGGA)n. To our knowledge there has been no large-scale study in FRDA patients to determine the frequency of interruptions in GAA repeat expansions. Therefore, we have investigated this in 245 FRDA patient and carrier DNA samples.

Aims: To address the question 'Do most FRDA patients have pure GAA repeat expansions?'

Methods: 245 FRDA patient and carrier DNA samples were amplified by long-range GAA repeat PCR and analysed by MBoII restriction enzyme digestion together with TP-PCR analysis.

Results: Our results demonstrate that the vast majority (87%) of FRDA GAA repeat expansions do not contain significant sequence changes that would result in abnormal MboII digestion profiles, indicating that they are primarily pure GAA repeats. However, a large number of samples (65%) do show small sequence variations at the 3' end of the GAA repeat sequence as detected by TP-PCR.

Conclusion: These results have specific implications in our understanding of FRDA disease progression and the more general understanding of trinucleotide repeat disease characteristics.

S2-P21

Category: Molecular Neuroscience

Regulation of LRRK2 phosphorylation in immune cells

Nazish I, Warner T, Hardy J and Bandopadhyay R

Affiliations: Department of Molecular Neuroscience and Reta Lila Weston Institute of Neurological Studies, 1, Wakefield Street, WC1N 1PJ

Background: Mutations in the *LRRK2* gene are commonly linked to familial Parkinson's disease (PD) and LRRK2 risk variants are also associated with idiopathic PD. LRRK2 is also linked to cancer, leprosy and Crohn's disease. LRRK2 protein harbours active GTPase and kinase activities and is expressed variably in several cell types with higher levels observed in immune cells. How LRRK2 dysfunction causes PD remains ambiguous.

Aims: To establish a link between LRRK2 dysfunction and signalling mechanisms in RAW264.7 cells and the pathological processes in PD.

Methods: Using RAW264.7 cells, we tested LRRK2 phosphorylation dynamics following treatment with LPS, paraquat, hydrogen-peroxide and also after inhibition of LRRK2 kinase activity using LRRK2-IN1. LRRK2 phosphorylation at different phospho-sites was monitored using immunoblotting with specific antibodies. Statistical significance was analysed using ANOVA and t-test using Graph-PAD prism.

Results: We observed significant upregulation of LRRK2 phosphorylated at Ser935 (and not Ser910) with LPS treatment from 2hr-24hr time points. A dose dependent increase of phosphorylation of LRRK2-Ser935 was observed after treatment with LPS and paraquat. Treatment with paraquat only showed downregulation of LRRK2 levels. Treatment with hydrogen peroxide (0.2-0.6mM) for 1 and 3hrs did not alter the phosphorylation levels of LRRK2-Ser935.

Conclusion: 1) LPS stimulates phosphorylation of LRRK2 in RAW264.7 cells. 2) Treatment of RAW264.7 cells with LPS and paraquat induced LRRK2 phosphorylation even further whilst treatment with PQ only decreased LRRK2 levels.

S2-P22

Category: Molecular Neuroscience

A new gene causing primary familial brain calcification (PFBC)

Lucia Schottlaender[1,3] and Henry Houlden[1,2]
on behalf of the PFBC research team

Affiliations: [1]Department of molecular neuroscience, UCL Institute of Neurology
[2]MRC centre for neuromuscular disorders, UCL Institute of Neurology
[3]Dubowitz neuromuscular centre, UCL Great Ormond Street Institute of Child Health

Background: PFBC or Fahr's disease constitutes a heterogeneous neurodegenerative disorder that presents with calcium deposits in the brain. The condition is mostly dominantly inherited although rarer recessive families have been reported. Four genes have been linked to dominant PFBC: *SLC20A2, PDGFRB, PDGFB and XPR1.*

Aims: To investigate the cause of PFBC in recessive families.

Methods: We excluded secondary causes of brain calcification and mutations in known genes in 2 large independent consanguineous families presenting with dystonia, learning difficulties and cerebellar ataxia. We then genotyped 3 affected and 2 unaffected subjects on a SNP array and performed exome sequencing on the proband.

Results: Three regions of homozygosity were found in chromosomes 10, 13, and 21. The bioinformatics analysis of the exome, targeted homozygous regions, filtered rare, putative pathogenic variants; and detected a homozygous nonsense variant in a gene that encodes a junctional molecule with endothelial functions. The variant segregated with disease in both families. A western blot in a fibroblast cell line of our proband showed absence of the protein in homozygous state compared heterozygous and controls. We developed a mouse model and tested knock-out mice for fine motor coordination and locomotion. The animals presented mild difficulties in beam walking test and gait abnormalities when compared to wild type.

Conclusion: We unravelled the cause of a severe neurological disorder. We were able to confirm the absence of the protein in a fibroblast cell line and we demonstrated impaired gait in a mouse model.

S2-P23

Category: Molecular Neuroscience

Probing activity-dependent dynamics of perisynaptic astrocytic processes using super-resolution.

Tarmier W, Reynolds J, Heller J

Affiliations: Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology.

Background: Thus far, it has been difficult to image astrocytes as both the synapse and the perisynaptic astrocytic processes (PAPs) are typically smaller than the diffraction-limited resolution of light microscopy (200-300 nm). Super-resolution (SR) imaging techniques, such as direct stochastic optical reconstruction microscopy (dSTORM) and expansion microscopy (ExM), can circumvent the optical diffraction-limit and offer ease-of-use and flexibility not seen in electron microscopy. This approach for PAPs visualisation may be revelatory of the activity-dependent dynamics *in situ*.
Aims: To study the activity-dependent dynamic changes of the PAPs using SR techniques.

Methods: Cell and brain slice cultures were generated and immunocyto- and immunohistochemistry were performed to label key synaptic and astrocytic components. Astrocytes were manipulated to express a membrane-bound fluorescent label or filled with tdTomato to allow gross morphology visualisation. Imaging consisted of fluorescence microscopy and dSTORM, exploiting the detection of the fluorescence emission of single fluorophores to reconstruct a super-resolved image. ExM was performed to physically expand tissue and increase the size of imaged structures.

Results: ExM was successfully employed in slice cultures, expanding tissue by a factor of 2.5 – 4 times. Fluorescence microscopy of expanded slices demonstrated nanoscopic structures in the astrocytic arbor. dSTORM revealed the presence of thin PAPs that were not visualised as clearly in widefield images.

Conclusion:SR reveals PAPs with resolutions not typically achievable in standard fluorescence microscopy. Further study of the RNA molecule nanostructure in PAPs will be undertaken by extending ExM procedures to focus on the localisation of long noncoding RNAs.

S2-P24

Category: Molecular Neuroscience

Genome-wide differential DNA methylation profiles from pre-mortem Creutzfeldt-Jakob disease blood

Luke Dabin[1], Holger Hummerich[1], Rachel Raybould[2], John Collinge[1], Emmanuelle Viré[1], Simon Mead[1]

Affiliations: [1] MRC Prion Unit, University College London, London, United Kingdom
[2] Institute of Psychological Medicine & Clinical Neurosciences, Cardiff University, Cardiff, Wales

Background: Epigenetic modifications occur at the level of DNA, chromatin and RNA, and regulate the action of genes temporally and contextually. Of these modifications, changes in DNA methylation have recently been implicated in several forms of dementia. Such diseases share with prion diseases a trend towards sporadic, late-onset cases characterised by protein dysmetabolism and progressive loss of neurons.

Aims: Here we investigate genome-wide DNA methylation in the blood of sporadic prion disease patients compared to healthy control subjects. By defining changes in the blood methylome, we aim to contribute to differential diagnosis, prognosis and better understanding of the disease's pathophysiology.

Methods: Pre-mortem blood samples from 116 sCJD patients were matched by age and sex with 111 controls. Genomic DNA was extracted and bisulphite treated, then hybridised to the Illumina Infinium 450K array. Array intensity files were imported into R and processed using ChAMP. A linear regression model including age and sex as covariates was used to calculate percentage change in methylation.

Results: Initial analyses highlight significant differences in DNA methylation at 25 sites between cases and controls. Decreased methylation at some of these sites appears to correlate with disease severity.

Conclusions: Studies of neurodegenerative disease have yielded both concordant and discreet methylation profiles between blood and brain tissue. By defining changes in the blood methylome of sCJD we aim to contribute to differential diagnosis, prognosis and understanding pathophysiology of the diseases. These results may be relevant to other neurodegenerative disorders involving propagation of proteopathic seeds.

S2-P25

Category: Molecular Neuroscience

Validating unannotated intergenic regions identified in human brain using annotation-agnostic eQTL mapping analyses

Regina Reynolds[1], Sebastian Manuel Guelfi[1], Karishma D'Sa[1,2], Juan Botia[1], UK Brain Expression Consortium, Michael Weale[2], John Hardy[1], Jana Vandrovcova[1] & Mina Ryten[1,2]

Affiliations: [1]Department of Molecular Neuroscience, University College London (UCL)
[2]Department of Medical & Molecular Genetics, King's College London (KCL)

Background: Gene annotation is the process of defining transcript structures and determining their function. The integrity of gene annotation is crucial, with any deficiencies propagated into downstream analyses. Current evidence suggests that annotation of the brain transcriptome remains incomplete, with current estimates from human frontal cortex RNA sequencing experiments detecting ~10Mb of transcribed intergenic sequence. However, the extent and functional significance of intergenic transcription in human brain is unclear. To address this question, annotation-agnostic eQTL mapping on whole transcriptome RNA-sequencing data obtained from the putamen and substantia nigra of 117 neuropathologically normal, post-mortem brains was performed. A total of 1236 eQTL-regulated unannotated transcribed intergenic regions were identified, and further characterised based on split read information, co-expression with a nearby gene and proximity to that gene.

Aims: To biochemically validate and functionally characterise a representative subset of the 1236 novel transcribed intergenic regions identified.

Methods: Validation and functional characterisation of 8 representative transcribed intergenic regions was performed across 7 putamen samples, using RT-PCR, Sanger sequencing and manual curation of open reading frames.

Results: We confirmed the presence of all transcribed intergenic regions, while functional characterisation indicated they were noncoding. Common to all validated regions was evidence of split read data across more than one sample.

Conclusion: This work demonstrates the validity of the annotation-agnostic approach, with implications for diagnostics and the interpretation of neurological GWAS hits.

S2-P26

Category: Molecular Neuroscience

Metabolomics profiling used as a tool to identify new biomarkers in sporadic inclusion body myositis

Wongsinin T., Machado PM.

Affiliations: MRC centre of Neuromuscular Disease, UCL Institute of Neurology

Background: Sporadic inclusion body myositis (IBM) is an acquired muscle disease with overlapping pathology of inflammation, degeneration and mitochondrial abnormalities. The primary cause and pathogenesis have remained unclear and there is still no effective treatment for IBM. We propose a metabolomics approach for obtaining a comprehensive picture of the metabolome and mapping metabolites to their key biochemical pathways. Metabolomic profiling can help to gain insight into the pathogenesis of the disease and also to identify disease biomarkers, making it an attractive tool for studying IBM.

Aims: To determine metabolic abnormalities in IBM in order to help elucidate the pathogenesis of the disease and to determine potential disease biomarkers that could be used in the future for diagnostic and disease monitoring purposes.

Methods: The serum metabolites from patients with IBM (n=35) and normal controls (n=56) were compared using the metabolomics platform created by Metabolon®. Tandem flow-injection targeted mass spectrometry will be used to quantify levels of metabolites in each serum sample. A total of 1364 biochemicals were analysed.

Results: We expect to identify a metabolomics signature in IBM. These findings will contribute to our knowledge about the disease, its pathogenesis and they may have potential diagnostic or monitoring implications in the future.

Conclusion: Metabolomic profilings was used to determine metabolic abnormalities and identify new biomarkers for sporadic IBM in this study.

S2-P27

Category: Animal research

Investigating the effects of segmental trisomy of mouse chromosome 17 on Alzheimer's disease pathology in the J20 AD mouse model

E Rhymes, J Tosh, F Wiseman

Affiliations: Department of Neurodegenerative Diseases, UCL Institute of Neurology

Background: All individuals with Down syndrome (DS) develop the histopathology of Alzheimer's disease (AD), including Amyloid-β plaques and Tau neurofibrillary tangles. DS results from trisomy of human chromosome 21 (Hsa21), on which the amyloid precursor protein (APP) gene lies. Duplication of APP drives Amyloid-β accumulation. However, despite having the pathology, not everyone with DS develops the associated clinical symptoms of AD, suggesting a potentially protective effect of trisomy.

Aims: To determine whether segmental trisomy of mouse chromosome 17, which is syntenic for a region of Hsa21, affects the build-up of AD pathology in the J20 AD mouse model.

Methods: Analysis of cortical and hippocampal tissue of J20 mice crossed with mice with three copies of chromosome 17 (Dp17Yey) at 6 and 12 months of age, using Amyloid-β ELISA, Western blotting and immunohistochemistry (IHC) techniques.

Results: IHC results show no significant difference in Amyloid-β coverage in the cortex or hippocampus between J20 mice and Dp17Yey/J20 crosses at 6 or 12 months. There is no difference in Amyloid-β peptide levels between J20 and Dp17Yey/J20 crosses at 6 months (awaiting 12 month data).

Conclusion: Duplication of the 19 genes present on the Hsa21-syntenic region of mouse chromosome 17 has no effect on AD pathology presentation, suggesting that potential protective effects of Hsa21 trisomy arise from duplications of other genes.

S2-P28

Category: Animal Research, Electrophysiology

Chemogenetic dissection of the mechanisms of secondary epileptogenesis

Weston MJ, Kullmann DM

Affiliation: Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology

Background: Epilepsy can be a devastating disease for individuals and presents a huge burden on society. Focal epilepsies frequently become treatment resistant over time due to the process of secondary epileptogenesis where the primary ictal focus induces a more distributed network and new independent epileptic foci.

Aims: To investigate whether secondary epileptogenenic foci are generated by repetitive seizures emanating from the primary focus during established epilepsy, or are formed independently during the induction of epilepsy but mature latently.

Methods: A seizure model comparable to human temporal lobe epilepsy is generated by injecting rats with intra-amygdala kainic acid to stimulate status epilepticus, and induce a seizure focus in the ipsilateral hippocampus. The local field potentials of bilateral hippocampi are recorded continuously for up to 6 months with wireless transmitters. A mutated human muscarinic receptor, responding only to the otherwise metabolically inert Clozapine-N-Oxide (designer receptor exclusively activated by designer drug (DREADD)), is focally transduced into excitatory neurons in either the primary or secondary ictal foci to suppress their activity while preserving normal brain function elsewhere. Administering CNO allows separation of the effects of ictogenesis from subsequent spontaneous seizures on secondary epileptogenesis

Results: Generation of the seizure model and optimisation of the chemogenetic tools are ongoing. Immunohistochemistry demonstrates that our optimised DREADD expresses well in excitatory neurons of the hippocampus. Initial tests show that acute administration of the DREADD agonist influences baseline local field potentials. Investigation of the effects of chronic administration are continuing.

S2-P39

Category Animal research

Human, fly and cell models of riboflavin transporter neuronopathy

Andreea Manole, Zane Jaunmuktane, Amelie Pandraud, Michael G. Hanna, Mary Reilly, Dimitri M. Kullmann, James E.C. Jepson and Henry Houlden

Affiliations: UCL Institute of Neurology, Queen Square, London WC1N 3BG

Background: The Brown-Vialetto-Van Laere syndrome (BVVLS) is a riboflavin transporter deficiency neuronopathy that represents a phenotypic continuum of motor, sensory, and cranial nerve neuronopathy. Most infants with this condition rapidly become ventilator-dependent and die during childhood. Mutations in two riboflavin transporter genes, *SLC52A2* and *SLC52A3*, have recently been shown to underlie a number of severe cases of BVVLS.

Aims: Our aims were to investigate: A) the scope of mutations occurring in these genes; B) the neuropathological features of two confirmed *SLC52A3* cases; C) the *in vitro* effects of *SLC52A2* mutations on cellular energy metabolism and mitochondrial function in fibroblasts of patients; and D) the *in vivo* consequences of the loss of the *SLC52A3* homologue in the fruit fly, *Drosophila melanogaster*.

Methods: We used Sanger sequencing to screen 132 patients exhibiting cranial neuropathies and sensorimotor neuropathy +/- respiratory insufficiency. Immunohistochemistry was performed on formalin-fixed, paraffin embedded brain and spinal cord tissue from two patients. We then performed functional assays and measured activities of mitochondria respiratory complexes in patients with *SLC52A2* mutations. We also employed an RNAi-mediated gene knockdown of the *Drosophila SLC52A3* homologue to recapitulate the loss-of-function phenotype of BVVLs.

Results: We identified a total of eight *SLC52A2* and fourteen *SLC52A3* pathogenic mutations, fourteen of which were novel. Two cases with confirmed *SLC52A3* mutations showed classical pathology of mitochondrial disease with symmetrical distribution of destructive legions in the brain stem and spinal cord. Mitochondrial respiratory complex I and complex II activity were decreased in *SLC52A2* mutation patients and carrier fibroblasts as a consequence of a deficit in riboflavin, FAD and FMN status confirmed by HPLC. Global knockdown of the *Drosophila* riboflavin transporter homologue revealed similar mitochondrial deficits in complex I activity and riboflavin, FMN and FAD levels. In addition, the flies had severely reduced life span and locomotor activity, phenocopying the patients' pathology. These features could be rescued by an ester of riboflavin.

Conclusions: Overall our findings confirm the pathogenetic role of *SLC52A2* and *SLC52A3* in BVVLS, and thus have important clinical and therapeutic implications.

S2-P30

Category Animal research

Title Mouse models of Down syndrome modify Alzheimer disease phenotypes in a novel mapping cross

Justin L. Tosh[1], Ellie Rhymes[1], Suzanna Noy[1], Karen Cleverley[1], Matthew Rickman[1],
Eva Lana-Elola[2], Sheona Watson-Scales[2], Victor L.J. Tybulewicz[2], Elizabeth M. C. Fisher[1], Frances K. Wiseman[1]

Affiliations: [1]Department of Neurodegenerative Disease, UCL Institute of Neurology
[2]The Francis Crick Institute

Background: Down syndrome (DS) occurs due to an extra copy of Human chromosome 21 (Hsa21), causing abnormal gene dosage and a greatly increased risk of developing Alzheimer's disease (AD). The amyloid precursor protein (APP) gene is found on Hsa21, and inheriting three copies of this gene alone is sufficient to cause early onset AD. However, Hsa21 genes other than APP likely influence AD-DS phenotypes and pathogenesis.

Aims: We aimed to discover and investigate genes on chromosome 21 which interact with AD phenotypes using mouse models.

Methods: We separately crossed two segmentally trisomic mouse models of DS with the 'J20' *APPSwInd* transgenic mouse model of APP/Aβ pathology which develops amyloid plaques by 5 months of age. We compared disease phenotypes between animals transgenic for *APP* and their littermates with *both APPSwInd* and segmental trisomy of DS genes.

Results: In this study, we demonstrate that double mutant animals carrying the *APPSwInd* transgene and trisomic for 37 mouse orthologues of genes on Hsa21 (excluding mouse *App*) between *Mis18a* and *Runx1* exhibit a significant reduction of Aβ42 aggregation and deposition and a dramatic increase in sudden death compared to J20 littermates. The second cross of J20 and a mouse model trisomic for 42 mouse gene Hsa21 orthologues between *Setd4* and *Zbtb21* resulted in a rescue of the sudden death phenotype in Trisomy;J20 double mutants compared to their J20 littermates. A third cross between J20 and a DS model trisomic for 19 Hsa21 orthologues between *Umodl1* and *Rrp1b* caused no identifiable modification to measured J20 AD phenotypes.

Conclusion: These data combined (1) support evidence for complex multi-gene interactions between Hsa21 genes and AD pathogenesis, and (2) highlight the potential of using mouse models to investigate genes which, when trisomic, cause AD-DS.

S3: Session 3 (10:35-11:25)

S3-P01

Category: Electrophysiology

Median filtering: A simple method for reducing spike contamination of local field potentials

Steven Jerjian[1], Stephan Waldert[1], Roger Lemon[1] & Alexander Kraskov[1]

Affiliations: [1]Sobell Department of Motor Neuroscience & Movement Disorders, UCL Institute of Neurology, Queen Square, WC1N 3BG, London, UK

Background: Neuronal spiking activity and local field potentials (LFPs) are usually separated from broadband recordings via linear bandpass filters, as they may carry different information about underlying neuronal dynamics. However, spike components can survive low-pass filtering[1], leading to inflated LFP power and artefactual spike-LFP correlations[2,3]. We systematically tested whether sliding median filtering in the time domain after spike detection could provide a robust approach for separating LFP and spiking activity.

Methods: Initial simulations were based on a previous study in which 100 datasets of "noise" ($1/f^{\alpha}$ pink noise, α=1.4) and "noise+spikes" (same noise plus spike waveforms extracted from recorded neuronal data) were created[1]. FFT amplitudes across pairs of "noise" vs. "noise+spikes" were compared before and after spike removal, with p-values used to fit a risk zone curve for spike contamination in an LFP frequency vs. spike rate plane. A real dataset was comprised of recordings in primary motor cortex of a rhesus macaque performing a reach-to-grasp movement task[4]. In a second set of simulations, spike bursts of up to 5 spikes were locked to particular phases on each cycle of a regular 20Hz sinusoidal oscillation, before being added to pink noise as before. Phases were drawn from a randomly generated Von Mises distribution (zero mean, k = 10). Phase locking values at spike times were calculated as the argument of the Hilbert transform of narrow bandpass filtered signals. Spiking activity was always identified by high-pass filtering and thresholding[5]. A sliding median filter (width 3ms) was applied to 1.5ms windows around detected spikes.

Results: Spectral power <300Hz attributable to spike contamination was significantly dampened following median filtering. This shifted the risk zone for spike contamination towards higher LFP frequencies, and improved spectral coherence estimates between artificial signals. Artificial phase locking at LFP frequencies introduced by residual spike waveforms in both simulations was eliminated following median filtering. In the real dataset, median filtering reduced gamma LFP power (60-100Hz).

Conclusion: This study demonstrates the potential use of median filtering as a better alternative to linear filters for separating spikes and LFP. This simple method easily removes spikes from the signal with minimal artefact introduction and does not require spike sorting. However, as the median filter does not preserve temporal order information within the window where it is applied, further studies may investigate more advanced median filters to improve retention of desired signal components.

S3-P02

Category: Electrophysiology

The reduction of LGI Trans-Synaptic Protein influences in vitro and in vivo neuronal circuits

Lugara' E.'[1], Chabrol E.[1] and Walker M.[1]

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

Background: LGI1 (Leucine-Rich Glioma-Inactivated1) is a neuronal secreted trans-synaptic protein part of the ECM (extracellular matrix). LGI1 mutations lead to a familial form of temporal lobe epilepsy.

Aims*:* Our aim is to study the acute and acquired reduction of LGI1 in neuronal circuits and to understand how this affects synaptic transmission.

Methods: for *in vivo* experiments the perforant path stimulation model of chronic temporal lobe epilepsy was used. After 21days the ipsi- and contralateral hippocampi were removed and measured LGI1 concentrations by western blot. For *in vitro* experiments, cortical cultures were prepared from E18 rat. Cells were then transfected with a shRNA for LGI1 and their activity recorded by Microelectrode arrays (MEA) and by calcium imaging.

Results: *In vivo* experiments on epileptic rats show a sharp decrease of LGI1 concentrations three weeks after severe status epilepticus within the ipsilateral side of the hippocampus. Parallel *in vitro* experiments use a knock down approach delivered by lentiviral transfection to reduce LGI1 expression. MEA results show increased mean firing rate of transfected cultures. Complementary *in vitro* calcium imaging recordings also indicate that treatment with LV-shRNA-LGI1 increase the frequency of calcium bursts.

Conclusion: Our results show that LGI1 expression in hippocampus is altered after 21 days of chronic epilepsy in freely behaving rats. LGI1 concentrations directly influence spontaneous network activity and seizure-like activity *in vitro.*

S3-P03

Category: Electrophysiology

Recessive SCN4A loss of function in congenital myasthenic syndrome, congenital myopathy or fetal akinesia deformation sequence

Michael G. Thor[1,2*†], Michael G. Hanna[1,2], Francesco Muntoni[1,2,3], Roope Männikkö[1,2]

Affiliations: [1]MRC Centre for Neuromuscular Diseases, 8-11 Queen Square, London; [2]Department of Molecular Neuroscience, UCL Institute of Neurology, London; [3]Dubowitz Neuromuscular Centre, UCL Institute of Child Health, London

Background: *SCN4A* encodes $Na_V1.4$, the skeletal muscle sodium channel integral to action potential generation and propagation. While dominant gain of function mutations in *SCN4A* are a well-established cause of myotonia and periodic paralysis, the phenotypes associated with recessive loss of function are more diffuse.

Aims: We further explore recessive *SCN4A* mutations in disease.

Methods: Homozygous or compound heterozygous *SCN4A* mutations were identified in twelve families by whole-exome sequencing. $Na_V1.4$ channel variants were expressed in *Xenopus laevis* oocytes and HEK293 cells, and functionally characterized by two-electrode voltage clamp and patch clamp, respectively.

Results: Patients with congenital myopathy develop *in utero*- or neonatal-onset muscle weakness of variable severity. All patients carry at least one full loss of function mutation. Depending on clinical severity, mutant channels may confer a partial, near-complete loss of function, or complete loss of function on the opposite allele. Partial loss of function is caused by reduced current density, attenuated channel activation or enhanced fast inactivation.

These pathomechanisms are distinct from congenital myasthenic syndrome, wherein bi-allelic enhanced fast inactivation is believed to reduce channel availability after high-frequency stimulation.

Conclusion: Bi-allelic loss of function in *SCN4A* give rise to at least three clinical phenotypes on a spectrum of severity, from congenital myasthenic syndrome to fetal akinesia. The severity of channel dysfunction correlates with clinical severity. Two compound recessive loss of function mutations—[at least] one of which causes full loss of function—attenuates the action potential amplitude to a level insufficient to sustain normal muscle force.

S3-P04

Category: Motor Neuroscience

Mitochondrial dysfunction and abnormal calcium handling play a role in Hereditary Sensory Neuropathy Type 1

Wilson ER[1,2], Kalmar B[1], Kugathasan U[1,2], Clark AJ[4], Bennett DLH[4], Abramov AY[3], Reilly MM[2], Greensmith L[1,2]

Affiliations: [1]Sobell Department of Motor Neuroscience and Movement Disorders, [2]MRC Centre for Neuromuscular Diseases, [3]Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London, United Kingdom, [4]Neural Injury Group, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, United Kingdom

HSN-1 is a peripheral neuropathy most frequently caused by missense mutations in the *SPTLC1* or *SPTLC2* genes, which code for two subunits of the enzyme serine palmitoyltransferase (SPT). SPT catalyzes the first and rate limiting step of *de novo* sphingolipid synthesis. It has been shown that mutations in SPT cause a change in enzyme substrate specificity which results in the production of two atypical sphinganines, deoxysphinganine (DSp) and deoxymethylsphinganine (DMSp), rather than the normal enzyme product, sphinganine (Sp). Levels of deoxysphingolipids are elevated in the blood of HSN-1 patients and this has been proposed to cause the peripheral nerve damage characteristic of the disease, which affects both sensory as well as motor axons. However, the underlying pathomechanism of how deoxysphingolipids damage neurons remains elusive. Here, DSp and DMSp-mediated neurotoxicity was examined in primary mouse motor and sensory neurons, by assessing cell survival and neurite outgrowth following exposure to different concentrations of Sp, DSp or DMSp. The abnormal enzyme products were found to have a rapid and dose-dependent neurotoxic effect in primary neurons. We also explored the potential mechanisms that underlie deoxysphingolipid neurotoxicity, by characterizing mitochondrial function and changes in calcium handling. We found that mitochondrial dysfunction and calcium handling deficits may be key mediators of abnormal sphingolipid neurotoxicity, in both motor and sensory cell models. Specifically, we revealed mitochondrial abnormalities, signs of endoplasmic reticulum stress and dysfunction of store-operated calcium channels. We propose that early deficits in mitochondria and calcium handling may underlie deoxysphingolipid neurotoxicity and thus present potential therapeutic targets for HSN-1.

S3-P05

Category: Motor Neuroscience

Regional differences in the inflammatory and heat shock responses of spinal cord and cortical glia – could this explain the selective death of motor neurons in ALS?

Benjamin Clarke[1], Rebecca San Gil[2], Bernadett Kalmar[1], Jing Yip[1], Linda Greensmith[1].

Affiliations: [1]Sobell Department of Motor Neuroscience & Movement Disorders, UCL Institute of Neurology, Queen Square, London, WC1N 3BG, United Kingdom.
[2]Illawarra Health and Medical Research Institute, School of Biological Sciences, University of Wollongong, Northfields Ave, Wollongong, 2522, Australia.

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 spinal cord and cortical glia.

Methods: Primary mixed glial cultures were dissected from SOD1^{G93A}/WT P3 mice and maintained for 8 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, immunoblotting and immunofluorescence were performed to analyse changes in inflammatory markers iNOS and the Iκβ-α member of the NFκβ complex and heat shock proteins Hsp70 and Hsp27.

Results: Spinal cord glia consistently expressed higher levels of NO and Hsp27 than cortical glia. Although there were no regional differences in the expression of Hsp70, it was downregulated in SOD1^{G93A} cortical and spinal glia following exposure to heat shock. SOD1^{G93A} glia expressed higher levels of iNOS and pIκβ-α after LPS treatment.

Conclusions: There are regional difference in the expression of Hsp27 between spinal and cortical glia. Downregulation of Hsp70 in SOD1^{G93A} expressing cortical and spinal glia might contribute to motor neuron death in ALS.

S3-P06

Category: Motor Neuroscience

Sensorimotor Processing in Post-Stroke Fatigue

Annapoorna Kuppuswamy[1], Sasha Ondobaka[1], John Rothwell[1], William De Doncker[1]

Affiliations: [1]Sobell Department of Motor Neuroscience and Movement Disorders

Background:The primary behavioural consequence of the sensorimotor feed-forward system is the ability to predict the consequences of motor commands, which are then verified with incoming sensory signals to inform future action. A unique feature of the sensory prediction-verification process is the diminished processing of sensory re-afferents, known as sensory attenuation. A perceptual consequence of sensory attenuation is the feeling of effortlessness associated with simple self-generated voluntary action. My hypothesis is that fatigue may be a pathology of diminished sensory attenuation. In neurological fatigue, there is a significant increase in perceived effort and consequently a reduction in self-initiated voluntary activity, as simple tasks often require high effort. A reduction in self-initiated voluntary activity in the absence of motivational, motor or cognitive deficits commonly seen in neurological conditions may result from malfunction in the system that predicts the sensory consequences of action.

Aims: My PhD aims to investigate the underlying sensorimotor processing in chronic neurological fatigue post-stroke. Fatigue in neurological conditions does not normally arise from altered sensory afferent input, as is partly the case in the context of physical activities, but from deficits in central processing.

Methods: I have developed a variety of protocols to test this hypothesis in chronic fatigued stroke survivors and healthy participants. These protocols include a Transcranial Magnetic Stimulation Protocol, a Saccade Task, a Force Matching task and a measure of Perceived Effort.

S3-P07

Category: Motor Neuroscience

The pathomechanism of Hereditary Sensory Neuropathy type 1 (HSN-1) involves ER stress

Howard H[1], Wilson ER[1,2], Kalmar B[1], Kugathasan U[1,2], Reilly MM[1,2], Greensmith L[1,2].

Affiliations: [1]Sobell Department of Motor Neuroscience and Movement Disorders,
[2]MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, Queen Square, London, United Kingdom.

Background: Hereditary sensory neuropathy type 1 (HSN-1) is an autosomal dominant condition affecting sensory, motor and autonomic nerves. It is most commonly caused by mutations in *SPTLC1* and *SPTLC2*, encoding two subunits of serine palmitoyltransferase (SPT), which catalyses the first step in *de novo* sphingolipid synthesis. In HSN-1, the mutation causes a shift in the enzyme's substrate specificity, leading to the formation of abnormal deoxysphingolipids. The deoxysphingolipids are neurotoxic and are proposed to cause the neuropathy in HSN-1.

Aim: To explore the pathomechanisms of HSN-1, particularly examining the role of endoplasmic reticulum (ER) stress.

Methods: We generate two *in vitro* models of HSN-1:

i. Primary mouse motor neurons treated with neurotoxic deoxysphingolipids
ii. A novel model whereby primary mouse motor neurons are transduced with a lentiviral vector delivering wildtype and mutant *SPTLC1.*

Following basic characterization of these models, we examined ER stress using immunocytochemistry and Western blot for an ER stress protein BiP, known to be upregulated in ER stress.

Results: We observed a trend towards upregulated BiP expression using Western blots and immunohistochemistry. BiP was upregulated in both disease models, suggestive of ER stress present in these cultures.

Conclusion: Here, we characterize a novel model of HSN-1, using virally transduced motor neurons expressing the mutant enzyme. Furthermore, we provide evidence indicative of a role for ER stress in the pathomechanism of HSN-1.

S3-P08

Category: Motor Neuroscience

Characterising the Effect of the Chronic Delivery of Glial-Derived Neurotrophic Factor (GDNF) to Motor Neuron Axons in Health and Disease

McLaughlin M, Schiavo G, Tosolini AP

Affiliations: Sobell Department of Motor Neuroscience & Movement Disorders, UCL Institute of Neurology

Background: Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease of the motor system, which ultimately causes motor neuron (MN) death. Pre-clinical investigations have used GDNF as a candidate therapeutic option. It is well established that axonal transport is impaired in ALS, however, the precise effect that GDNF has on MN axonal transport is unknown.

Aims: Investigate the effects of axonally– delivered GDNF on 1) axonal transport dynamics; and 2) pro-survival signalling.

Methods: Ventral horn cells obtained from embryonic SOD1G93A and wild-type mice were cultured in microfluidic chambers to maintain fluidic isolation between MN somata and axon terminals. Cultures were monitored for sufficient axonal growth into the axonal compartment to determine the optimal day for GDNF treatment to begin. GDNF (50ng/ml) was chronically added to the axonal compartment over 3-4 days. Retrograde transport of signalling endosomes was then assessed via confocal microscopy of a fluorescently-tagged tetanus toxin fragment in MN axons. Pro-survival effects on wild-type somata were also assessed by western blot.

Results: Day six in vitro proved to be optimal for sufficient axonal growth. Mean track velocities of signalling endosomes increased after GDNF treatment, appearing to have a greater effect in the SOD1G93A cultures. There was a down-regulating trend of somatic pro-survival signalling pathways observed after treatment.

Conclusions: Chronic axonally delivered GDNF treatment appeared to influence the signalling dynamics of axonal transport in mixed primary ventral horn cultures. However, further experiments are required to determine the precise influence that GDNF-treatment has on axonal transport dynamics as well as pro-survival signalling.

S3-P09

Category: Motor Neuroscience

Development of small molecule modulators of the heat shock response for the therapeutic use in ALS

Nicholas Wisbey, Bernadett Kalmar and Linda Greensmith

Affiliations: Sobell Department of Motor Neuroscience and Movement Disorders, UCL Institute of Neurology, Queen Square, London, WC1N 3BG, UK

Background: The pathogenesis of many neurodegenerative diseases, involves protein misfolding and aberrant protein handling. Heat-Shock Proteins (HSP's) ensure the correct folding of proteins and therefore are an attractive target for pharmaceutical development. Hydroximic Acid (HA) derivatives, such as arimoclomol, act as co-inducers of the heat shock proteins (HSP's). Arimoclomol has been shown to be protective in animal models of ALS and in a clinical trial on mutant SOD1 ALS patients.

Aims: We would like to develop follow up molecules to arimoclomol, with more potent HSP induction capacity and more effective blood brain barrier penetration.

Methods: Arimoclomol derivatives were designed and synthesized by LipidArt, our industry collaborator. Primary spinal cord motor neurons were treated with arimoclomol analogues under control, oxidative stress (H_2O_2), inflammatory stimuli (LPS) and heat shock conditions. Cell lysates were collected at 30 minute and 24-hour time points and expression of a range of Hsps were investigated using Western blot and immunohistochemistry.

Results: Heat shock induces expression of Hsp70 and our evidence shows that some of our compounds enhance this response. Mitochondrial heat shock proteins are not induced by heat shock but are upregulated by oxidative stress.

Conclusion: By the end of this project we hope to identify specific molecules that have HSP induction effects under specific ALS related stress conditions and are more potent than arimoclomol.

S3-P10

Category: Motor Neuroscience

Effect of fluoxetine on the effect of continuous theta-burst stimulation (cTBS) in the human motor cortex

Dias Amador, L.[1], Austin, D.[1], Li, L.[2], & Rothwell, J. C.[1]

Affiliations: [1] Sobell Department of Motor Neuroscience, UCL, UK.
[2]Faculty of Medicine, Imperial College, UK

Background: Transcranial Magnetic Stimulation (TMS) is a means of modulating cortical circuitry non-invasively, through an intact cranium. If delivered over the motor cortex it will elicit a motor evoked potential (MEP), a recordable change in electrical potential in the opposite limb. Repetitive stimulation can induce changes in MEP mimicking the phenomena of LTD and LTP.

Selective serotonin reuptake inhibitors (SSRIs) are a class of drugs that inhibit serotonin reuptake from the synapse and have shown promise in recent clinical trials to promote recovery after brain injury (Chollet, 2012). This may be caused by a mechanism known as Hebbian plasticity, and if it is indeed an effect, it may be detectable using TMS.

Aims: To investigate the effect of fluoxetine on the effect of continuous theta-burst stimulation in the human motor cortex, in healthy volunteers.

Methods: 31 healthy subjects, aged between 18-50, are being tested after receiving alternatively a single dose of 20mg fluoxetine or placebo. TMS is delivered to the motor cortex of the dominant hemisphere using an electro-magnetic coil, focusing on the hand area of the motor cortex. MEPs are recorded from the contralateral first dorsal interosseous (FDI) muscle. To this location, initially single pulses are applied to, followed by cTBS, with follow up single pulses over 30 minutes to measure the inhibitory effect of TBS.

S3-P11

Category: Motor Neuroscience

The control of body motion during a step

Matthew J. Bancroft[1], Brian L. Day[1]

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

Background: Lifting a foot from the ground to take a step destabilises the body. At the instant the stepping foot lifts the body is rarely positioned directly over the stance foot and therefore begins to fall sideways under the influence of gravity during the step.

Aims: Here we investigate how body motion is controlled during a step.

Methods: Subjects stepped to visual targets and the motion of the body during the step was recorded. Body motion was compared to a simulated model which was given the body's initial conditions when the stepping foot lifted and fell under the influence of gravity during the step.

Results: The body's initial conditions when the stepping foot lifted differed depending on the target location. When given these initial conditions, the model would typically overshoot the observed body motion. The addition of the torque generated about the ankle for each step resulted in accurate simulation of body motion, suggesting that the fall of the body during a step is modified by ankle torque. However, randomly shuffling the torques generated during different steps made little difference to simulated body motion. In contrast, shuffling the body's initial conditions substantially changed simulated body motion.

Conclusion: The results show that the body undergoes a controlled fall during a step. The body's initial conditions when the stepping foot lifts seem of critical importance in ensuring the body moves towards its intended target. By setting suitable initial conditions, an appropriate fall is initiated and the need for mid-step adjustments are minimised.

S3-P12

Category: Motor Neuroscience

In vitro models of Charcot-Marie-Tooth disease to investigate disease pathomechanisms

Verna Sarajarvi[1,2], Bernadett Kalmar[1], Mary M. Reilly[2] and Linda Greensmith[1,2]

Affiliations: *1) Sobell Department of Motor Neuroscience and Movement Disorders, 2) MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, Queen Square, London, WC1N 3BG, UK.*

Background: Charcot-Marie-Tooth disease (CMT) -causing mutations are found in genes encoding proteins with diverse cellular functions. It is possible that there may be common pathomechanisms shared between different forms of CMT, or conversely, there may be great specificity in the cellular changes caused by different mutations.
Aims: In this project we aim to investigate and compare the pathological changes induced by different CMT-causing mutations in two *in vitro* disease models; 1) patient fibroblasts and 2) primary motor neurons expressing mutations.
Materials and Methods: Human CMT patient (with mutations in *MFN2*, *MT-ATP6*, *OPA1*, *HSPB1*, *FIG4, SH3TC2* and *NEFL* genes) and control fibroblasts were obtained from the MRC Centre Biobank. Mitochondrial membrane potential was measured using tetramethylrhodamine methyl ester (TMRM). Two different types of viral backbones were tested and 3rd generation lentiviral vectors carrying wild-type and pathogenic forms of CMT-causing genes were generated for the transduction of mouse primary motor neurons.
Results: Patient fibroblasts carrying mitochondrial mutations (*MFN2*, *MT-ATP6* and *OPA1*) show a highly significant reduction in mitochondrial membrane potential. We have investigated two different viral backbones that can be used to transduce primary motor neurons, and identified a suitable backbone for constructing lentiviruses carrying different CMT-causing mutations.
Conclusion: Mitochondrial function is compromised in CMT patient fibroblasts carrying mutations in genes involved in mitochondrial function. We are currently developing our viral *in vitro* model of different CMT subtypes, which is suitable for investigating and comparing CMT pathomechanisms in primary motor neurons.

S3-P13

Category: Motor Neuroscience

Investigating FUS role in global and local translation in a mouse model for ALS

Francesca Mattedi[1], Nicol Birsa[2], Anny Devoy[2], Elizabeth Fisher[2], Giampietro Schiavo[2], Gabriella Viero[1], Pietro Fratta[2]

Affiliations: [1]Institute of Biophysics CNR, Trento, Italy
[2] UCL Institute of Neurology, Queen square, London, WC1N 3BG, UK

Background: ALS is a neurodegenerative disease characterized by the progressive loss of upper and lower motor neurons, resulting in motor impairment. FUS is an RNA binding protein and ALS-causing mutations in FUS determine its mis-localization from the nucleus to the cytoplasm. Mutations act through cytoplasmic gain of function, but the mechanism that leads to disease is unknown.

Aims: Here, we investigate the hypothesis that mutant FUS impairs global and local translation in motor neurons. Specifically, we test the impact of mutant FUS on the composition of translation machinery, the composition of RNAs being translated and the possible defects in transport of ribosomes along ALS axons.

Methods and Materials: We have used tissues and primary cultures from a novel ALS mouse model. Translation was investigated using polysome profiling and microfluidic devices allowed to physically isolate and study axons from cell bodies. Primary neurons transfected with GFP-tagged ribosomal proteins were analysed by confocal microscopy and live-cell imaging.

Results: Wild-type FUS co-sediments with polysomes in wild-type brains, while mutant FUS does not localise on these structures. This was observed together with alterations of the co-sedimentation profile of FMRP with polysomes. Immunocytochemistry on primary neurons suggests a contiguity and a possible interaction between FUS and FMRP.

Conclusion: Our results suggest that mutant FUS alters FMRP association with the translational machinery in a mouse model of ALS. We are currently investigating the possibility of this leading to a dysregulation of protein synthesis regulation or trafficking of ribosomes and associated mRNAs along axons.

S3-P14

Category: Motor Neuroscience

The Modulation of Task Dependent Actions via Putative Propriospinal Pathways

Azzopardi S[1], Bunday KL[1].

Affiliations: [1]Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, University College London

Background: The propriospinal network is an interneuronal system located at the mid-cervical levels (C3-C4), which transmits and alters descending commands for targeted reaching and grasping. Although first discovered in the cat, there is some debate concerning its functional importance in humans and primates. In humans, the propriospinal system can be studied indirectly by conditioning motor evoked potentials (MEPs), elicited by transcranial magnetic stimulation (TMS), with low-intensity peripheral nerve stimulation (PNS).

Aims: The aim of this project is to probe the contribution of the propriospinal system during different forms of skilled grasping, namely precision grip (PG) and whole hand grasp (WHG).

Methods: Low threshold PNS applied percutaneously to the ulnar nerve at the wrist was employed to condition FCR MEPs - elicited by TMS applied over the motor cortex – during wrist flexion alone, index and little finger abduction, PG and WHG. Central conduction and peripheral condition time were used to time the arrival of stimuli at the cervical spinal cord at five different ISI values: namely 0, -3, -4, -5 and -6.

Results: Data collection is currently ongoing, although initial results show that conditioned MEPs are differentially modulated by the type of grasp being performed.

Conclusion: Studying the propriospinal system in healthy humans will show how motor commands are updated at a spinal premotoneuronal level and could provide a novel pathway to target for neurorehabilitation following lesions of the central nervous system.

S3-P15

Category: Motor Neuroscience

ATTENTION AND FUNCTIONAL MOVEMENT DISORDERS: Its role in symptom generation and sense of agency

Anne-Catherine Huys MD[1], Mark Edwards PhD[2], Patrick Haggard PhD[3], Kailash Bhatia MD[1]

Affiliations: *1 Institute of Neurology, University College London, 2 Institute of Cognitive Neurosciences, University College London, 3 St George´s University, London.*

Background: Patients and doctors frequently face debilitating physical symptoms that remain unexplained and without clear treatment. The majority of these are of "functional" origin, also called psychogenic or psychosomatic.

Functional movement disorders are involuntary, abnormal movements, such as tremor or paralysis, that are illogical in terms of classical neurology. Intriguingly, they typically manifest when patients pay attention to them and disappear with distraction.

Aims: We hypothesise that misdirected attention brings about these abnormal, involuntary movements. Instead of focusing on the goal, on the desired outcome, patients direct their attention onto the movement itself, onto the mechanics of movement execution, thereby hampering its automatic execution.

We aim to imitate the abnormalities of functional movement disorders - impaired movement performance, decreased sense of agency and abnormal brain activation patterns - in unaffected individuals by getting their attention focused on movement execution. Conversely we aim to partially normalise these abnormalities in functional tremor patients by manipulating their attention onto the goal of the movement.

Methods/Patients: Patients with functional tremor, organic tremor patients and healthy controls) reach to a goal, while an additional task manipulates their attention onto the goal or the movement itself. The effect will be analysed in terms of movement performance, sense of agency and brain activation.

Results: By May I will have analysed the preliminary data.

Conclusion: If characteristics of functional movement disorders can be recreated in unaffected individuals and conversely improved in functional movement disorders by attentional focus manipulations, then such manipulations could offer an effective treatment strategy.

S3-P16

Category: Motor Neuroscience

Progressive myoclonus epilepsy linked GOSR2 mutations cause dendrite growth deficits, synaptic retraction and hyperactive synapses

Roman Praschberger[1], Simon Lowe[2], Nancy T. Malintan[1], Henry Houlden[3], Maria M. Usowicz[2], Shyam S. Krishnakumar[1,4], Dimitri M. Kullmann[1], James J.L. Hodge[2], James E. Rothman[1,4], James E.C. Jepson[1]

Affiliations: [1]Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, London, UK
[2]School of Physiology and Pharmacology, University of Bristol, Bristol, UK
[3]Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK
[4]Department of Molecular Biophysics and Biochemistry, Yale School of Medicine, New Haven, USA

Mutations in the Golgi SNARE protein GOSR2 cause progressive myoclonus epilepsy (PME). Despite GOSR2's known role in mediating ER to Golgi and intra-Golgi membrane fusion, it is unclear how these mutations result in a selective neuronal phenotype. We investigated this open question with a multi-stage approach and found SNARE dysfunction and reduced GOSR2 amounts at the molecular level. This translated into only a subtle decrease in Golgi trafficking rates, which neurons appeared particularly vulnerable to. Dendritic arbors were profoundly shortened and motoneuron synapses exhibited synaptic retraction and altered neurotransmitter release. Thus, besides providing overarching insights into the pathophysiology of GOSR2-PME, this study highlights how even subtle early secretory pathway deficits are magnified in dendritic development and suggests a critical role of the Golgi apparatus in presynaptic development and function.

S3-P17

Category: Clinical Neuroscience

Analysis of Copy Number Variants in Familial and Sporadic Parkinson's disease

Theresita Joseph[1], Jason Hehir[2], Manuela Tan[1], Wei Zhang[1], Henry Houlden[3], Steven Lubbe[4], Huw Morris[1]

Affiliations: [1]Department of Clinical Neuroscience, UCL Institute of Neurology
[2]National Hospital for Neurology and Neurosurgery, Queens Square, London,
[3]Department of Molecular Neuroscience, UCL Institute of Neurology,
[4]Feinberg School of Medicine, Northwestern University, Chicago

Background: Copy number variants (CNVs), involving duplications or deletions of DNA segments of varying length, are recognised to contribute to Parkinson's disease (PD) pathogenesis.

Aims: The present study investigated CNV prevalence in 191 PD patients from across the country (175 autosomal dominant, 3 autosomal recessive, 13 sporadic). Additionally, 10 PD patients with previously identified *PARK2* mutations were analysed to detect second mutations conferring compound heterozygous states.

Methods: Multiplex ligation-dependent probe amplification (MLPA) was used to identify CNVs in known PD genes, using SALSA P051 and P052 probe kits (MRC Holland), which contained probes for all exons of *SNCA, PARK2, UCLH1, PINK1, DJ-1, LRRK2* and *ATP13A2*. Raw data was analysed using GeneMapper Software, with deletion/ duplication boundaries delineated by ≤0.75 and ≥1.25 ratio values respectively.

Results: A total of 11 duplications/deletions in the PD genes *PARK2, SNCA*, *DJ-1* and *PINK1* were identified, indicating that 5% of our PD cohort possessed CNVs. Significant findings include 3 whole gene *SNCA* duplications, a heterozygous *PARK2* exon 2 deletion in a pseudo-dominant PD patient, a novel heterozygous *DJ-1* duplication of exons 2,3,5,6,7 and a novel homozygous *PINK1* deletion of exon 1.

Conclusions: Whilst further clinical and genetic information is required, our work emphasises the importance of CNV detection in PD, and contributes to work exploring the role of single heterozygous *PARK2* CNVs in PD risk.

S3-P18

Category: Clinical Neuroscience

Measurement of CSF hypothalamic peptides in frontotemporal dementia.

Heller C, Heywood W, Theodoridi A, Woollacott IOC, Warren JD, Mills K, Rohrer JD

Background: Frontotemporal dementia (FTD) is a progressive, neurodegenerative disorder with clinical and pathological heterogeneity. The main clinical FTD phenotypes are behavioural variant FTD (bvFTD), semantic dementia (SD) and progressive nonfluent aphasia (PNFA). One of the key clinical characteristics of bvFTD is disturbance in eating behaviour, which can be helpful in diagnosing bvFTD and differentiating it from Alzheimer's disease (AD). The aim of this study was to develop a hypothalamic peptide panel, focusing on measures known to be involved in appetite regulation, to gain a better understanding of the pathophysiology of FTD, and potentially leading to better fluid biomarkers.

Method: A peptide multiplex panel of 13 hypothalamic and 9 peripheral appetite regulating peptides was developed on a liquid chromatography coupled tandem mass spectrometry platform. Concentrations were measured in the CSF of the three clinical FTD phenotypes (bvFTD n=9, SD n=9, PNFA n=4) as well as AD (n=4) and healthy controls (n=6) and compared using non-parametric statistical tests.

Results: In five of the hypothalamic peptides there was a significant difference (expressed as pmol/300 µl) between controls and at least one of the FTD groups ($p<0.05$): neuropeptide W levels were significantly higher in all three groups: bvFTD (0.029), SD (0.034) and PNFA (0.039), controls (0.012); cerebellin was decreased in bvFTD (0.586) and SD (0.591) [controls 0.945], and cocaine-amphetamine regulated transcript was decreased in PNFA (0.359) and SD (0.359) [controls 0.575]; corticotropin-releasing hormone was decreased in bvFTD (0.007) [controls 0.011] and galanin was increased in PNFA (0.107) [controls 0.059]. There was also a trend of decreased levels of pro-orexin in bvFTD. There were also significant differences in two of the peripheral peptides in PNFA (insulin-like growth factor 1 and pancreatic polypeptide).

Conclusions: This pilot study shows changes in concentration of a substantial proportion of the hypothalamic peptides within the CSF in the FTD groups compared to controls. Further exploration on a larger clinically defined cohort will enable understanding of the differences in hypothalamic peptides in FTD and investigate whether such a panel could be used as a biomarker in FTD disease diagnosis, prognosis or stratification.

S3-P19

Category: Clinical Neuroscience

What is the role of the WDR45 gene in autophagy?

Daniel Cotfas

Autophagy is a cellular process involved in the turnover of materials and subcellular structures. WDR45 is a protein with a putative role in autophagy regulation, and mutations in WDR45 lead to disease. The function of the WDR45 protein has not been fully elucidated, and it is the focus of our investigations. It may act as a regulator of autophagy, possibly behaving as the scaffold for proteins involved in early autophagy to assemble. Patients with de novo WDR45 mutations are diagnosed with BPAN: beta-propeller protein associated neurodegeneration.
MRI scans of BPAN-patient brains exhibit iron accumulation in the substantia nigra and globus pallidus and generalised atrophy of cerebrum and cerebellum. Post-mortem brain sectioning reveals neurofibrillary tau tangles throughout the cortex, with mixed 3R-4R pathology similar to Alzheimer's disease. Certain mutations in WDR45 have also been implicated in Rett-like syndrome and epilepsy, further highlighting the implications of our project to neurodegenerative research at large.

Methods: BPAN-patient skin fibroblasts will be reprogrammed into induced pluripotent stem (iPS) cells, and differentiated into disease-relevant, region-specific cortical and dopaminergic neurons. Normal control and BPAN-patient fibroblasts, iPS cells, and neurons will be examined for changes in autophagy. Protein and RNA investigations will be undertaken in frozen post-mortem brain and in cultured cells using RT-qPCR and western blotting. Other autophagy-related mechanisms such as mitochondrial dysfunction and iron metabolism will also be examined.

Results: Investigations into WDR45 expression by western blot and RT-qPCR suggest reduced protein expression in BPAN-patient skin compared to normal controls, as well as reduced autophagic flux as assayed by comparing LC3 protein levels. This pattern extends into iPS cells and neural stem cells early in cortical differentiation, and is corroborated by immunocytochemical data. We plan to further investigate proteins involved in early autophagy, elucidate binding partners for WDR45, and describe the effects of WDR45 mutation on other proteins involved in autophagy.

As the pathophysiological mechanisms of WDR45 mutation are described, we will begin to understand the normal function of WDR45 in autophagy, and identify targets for clinical interventions in BPAN patients. Along with future research, our data will serve as a foundation to produce treatments, and positively affect the quality of life for patients with autophagy-related diseases.

S3-P20

Category: Clinical Neuroscience

Which brain regions are damaged in stroke patients with apraxia of speech?

Convery R[1], Price CJ[1]

Affiliations: [1]Wellcome Trust Centre for Neuroimaging, UCL

Background: Apraxia of speech (AOS) is a motor speech deficit involved in impaired planning of motor movements. The deficit is characterised by off-target articulation, sound distortions, and significantly slowed rate of speech. Research has suggested the involvement of a number of areas associated with AOS, including the premotor cortex, the anterior insula, and Broca's area. However, due to variability in lesion size, and commonly presenting co-morbid impairments, previous literature has failed to agree on a specific brain region associated with AOS.

Aims: To identify lesions in brain areas associated with AOS symptoms, in order to reveal possible neurological underpinnings of the disorder.

Methods: Patients from the PLORAS database were identified with symptoms of AOS, based on their scores on the Comprehensive Aphasia Test (CAT). Patients were selected if they displayed impaired repetition of complex words, slow picture description speed, with preserved sentence repetition and good written picture description. From the selected patients, lesion sites were then identified and qualitative differences in speech were noted from patient recordings.

Results: 16 patients were identified as having AOS symptoms. Patients displayed common lesion sites, including the premotor cortex (IFG opercula), putamen, and the tongue/larynx region of the motor cortex. Preliminary results from the patient recordings show that patients with more complete damage to the premotor cortex area, display more typical apraxic deficits.

Conclusion: AOS symptoms can be caused by damage to different brain regions that each play a distinct role in the speech production process.

S3-P21

Category: Clinical Neuroscience

Rich-Club Organisation and cognitive Performance in Clinically Isolated Syndromes

Ooi J[1], Grussu F[1], Collorone S[1], Prados F[1], Wheeler-Kingshott C[1], Ciccarelli O[1], Tur C[1]

Affiliations: [1]Department of Neuroinflammation, UCL Institute of Neurology

Background: Cognitive impairment is being increasingly recognised in patients with clinically isolated syndromes (CIS) but its underlying pathomechanism remains unknown. Structural connectivity is a growing field that endeavours to describe how the brain is connected anatomically. It considers the brain as a complex network, where “nodes” represent cortical areas and “edges”, the white matter fibres that connect them.

We hypothesise that cognitive impairment in CIS is driven by aberrations in structural connectivity, pertinently, those affecting the rich-club organisation, an important type of central network made up of strong associations between a subset of highly connected nodes.

Aim(s): We investigated whether changes to individual structural network parameters correlated with cognitive impairment in patients with CIS and whether they preferentially affected the rich-club organisation.

Methods/Patients: 19 patients and 12 controls underwent cognitive testing (symbol digit modalities test) and MRI scans (conventional and diffusion) at baseline. Probabilistic tractography was performed on diffusion scans using constrained spherical deconvolution. Tracts were subsequently parcellated to form connectomes which were then subjected to graph theory analysis. Relevant statistical evaluations between predefined measures were eventually performed.

Results/Conclusion: (Anticipated) Results in line with our hypothesis would strengthen the notion that disruption of structural connectivity patterns drives cognitive impairment in CIS. Using these as predictors alongside other established CIS prognostic factors will allow for better patient counselling, more judicious use of disease modifying treatments, and more representative inclusions into future research.

S3-P22

Category: Clinical Neuroscience

Prevention of Hypertensive Injury to the Brain by Intensive Treatment after IntraCerebral Haemorrhage: A Pilot Study (PROHIBIT-ICH)

Vishu Chakravarti[1], Professor David Werring[1,2,3]

Affiliations: [1]Department of Stroke Medicine, UCL Institute of Neurology
[2]Stroke Research Centre, University College London

[3]Stroke Association and British Heart Foundation

Background: Intracerebral hemorrhage has a high recurrence rate with patients facing poorer cognitive and physical impairments than the former episode. Research has shown benefits of acute blood pressure (BP) management post-ICH. However, there is a lack of clarity on how it protects the brain, how much to lower it, for how long or how best to manage it chronically. Telemetric BP home monitoring is a promising BP management method in TIA attacks but hasn't been tested in ICH patients.

Aims: To understand whether intensive lowering of BP using telemetric home monitoring in survivors of ICH is feasible, safe and effective in reducing brain injury.

Methods: It's a multi-centre RCT comparing a strategy of intensive BP treatment (target 120/70mm Hg) guided by telemetric home monitoring, versus standard care, in 100 ICH survivors. Outcome Measures include feasibility (consent rate, dropout from the intervention arm, patient approval), safety (adverse events) and exploratory efficacy (incidence of micro-bleeds, change in white matter hyper-intensity volume and cognitive function, recurrent cerebrovascular events over 1 year).

Results: Still in the beginning stages of the trial, results are yet to be achieved.

Conclusion: If successful, it'll be a precursor for a larger definitive trial. Also, the intervention should allow survivors of ICH to know, understand, and manage their own BP to prevent strokes and cognitive impairment, and improve outcomes.

S3-P23

Category: Clinical Neuroscience

The impact of Exenatide on motor complications in Parkinson's disease.

Pao-Sheng Chang[1], BSc, Dilan Athauda[1], MRCP, Kate Maclagan[2], PhD, Simon S. Skene[2], PhD, Martha Bajwa-Joseph[2], PhD, Dawn Letchford[2], , Steve Hibbert Luca Zampedri[3], MSc, Iciar Aviles-Olmos[1], PhD, Prof Thomas T. Warner[5], FRCP, Prof Patricia Limousin[1], MD, Prof Andrew J. Lees[1], FRCP, and Prof Thomas Foltynie[1], PhD.

Affiliations: [1]Sobell Department of Motor Neuroscience, UCL Institute of Neurology & The National Hospital for Neurology and Neurosurgery, Queen Square, London, WC1N 3BG; [2]UCL Comprehensive Clinical Trials Unit (UCL CCTU); [3]Leonard Wolfson Experimental Neuroscience Centre (LWENC), Queen Square, London, WC1N 3BG; [4]Institute of Nuclear Medicine, University College London Hospitals NHS Trust; [5]Queen Square Brain Bank, 1 Wakefield Street, London

Background: Motor fluctuations and dyskinesia are significant complications of continued levodopa therapy in Parkinson's disease (PD). Exenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist, has neuroprotective effects in experimental models of PD and treatment was associated with persistent improvements in motor function in a small, open label Exenatide-PD trial. We assessed motor complications using the MDS-UPDRS (Part4), Unified Dyskinesia Rating Scale (UDRS) and 3-day Hauser diary.

Aims: 1. Evaluate and critique the various scales used to identify motor complications at baseline 2. Assess the effect of Exenatide exposure on motor complications in PD

Methods:
Data regarding motor complications was collected at baseline and at 12-weekly intervals. Through SPSS, bivariate analysis was applied to calculate the scale-scale correlations at baseline, and longitudinal data was analysed via either ANCOVA or non-parametric test.

Results:
1. In bivariate analysis, MDS-UPDRS and 3-day Hauser diary displayed strong correlations for measuring dyskinesia severtiy and the off-time durations at baseline.
2. Data collected at baseline from each scale did not show significant differences between Exenatide and placebo groups.
3. In MDS-UPDRS Part 4, UDRS and 3-day Hauser diary, we observed the trends of clinical improvements rather than statistical improvements.

Conclusion:
Although the results did not reach statistical significance, data seemed to indicate that patients had less severe motor complications in the Exenatide group. Also, the analysed Exenatide-PD trial is able to provide plausible evidence about the efficacy of Exenatide against PD motor complications.

S3-P24

Category: Clinical Neuroscience

Neuropsychological outcome in children with relapsing inflammatory demyelinating syndrome

María Camila Pantoja[1], Adam Kuczynski[2], Seona Granville[2], Olga Ciccarelli[1], Cheryl Hemingway[3], Yael Hacohen[1,3]

Affiliations: [1]Department of Neuroinflammation, Queen Square MS Centre, UCL Institute of Neurology, London, UK
[2] Department of Neuropsychology, Great Ormond Street Hospital for Children, London, UK.
[3] Department of Paediatric Neurology, Great Ormond Street Hospital for Children, London, UK.

Background: Acquired demyelinating syndromes (ADS) represent acute neurological illnesses characterized by deficits persisting for at least 24 hours and involving the optic nerve, brain or spinal cord, associated with regional areas of increased T2 signal on conventional MRI. The majority of children presenting with acute demyelination will have a transient/monophasic illness but 15-46% of children will have a relapsing, more chronic disease (called relapsing inflammatory demyelinating syndrome (RDS)), and may develop progressive disabilities. The natural history paediatric RDS is less clearly defined, part due to relatively small sample size but also due to age-related differences in presentation and pertubation of age expected brain develepment during the disease course.
In this study we evaluated the neuropsychological profile of children with RDS. We aimed to identify key features for each RDS, and additionally test if the age at disease onset and the disease duration impact the neuropsychological outcome.

Methods: A total of 38 patients with RDS were retrospectively studied. Final RDS diagnosis was stratified to MS (n=27), AQP4-Ab NMOSD (n=2), MOG-Ab associated disease (n=5) and antibody-negative RDS (n=4). All patients had neuropsychological assessment at Great Ormond Street children Hospital (London) between 2010-2016, as part of their routine clinical management. The following cognitive domains were assessed; Intellectual function (Wechsler Intelligence Scale for Children IV, WISC-IV), Academic attainments (Wechsler Individual Achievement Test II, WIAT-II), visual-motor function (Beery-Buktenica Developmental Test), memory, attention and executive function.
Statistical analysis was performed using commercially available software GraphPad Prism 6 [GraphPad Software Inc]). Non-parametric statistical tests (Mann-Whitney tests) were used for continuous distributions, and Fisher's exact tests for nominal data. Patients with AQP4-Ab NMOSD, MOG-Ab associated disease and Ab negative RDS were grouped together and were compared to the MS group for statistical analysis. The study was approved by Great Ormond Street Hospital Research and Development Department (reference: 16NC10).

Results: Patient with MS were older than the patients with non-MS. At least one abnormal neuropsychological test was reported in 25/38(66%) of the children. No differences were detected between the MS and non-MS groups (16/27 vs 9/11, p=0.27). The non-MS group was found to have lower mathematical reasoning (Median difference 21, 95% CI 1-29, p=0.034) and slower speed of handwriting (median difference 3, CI 0-6, p=0.028). MS group scored lower in the Visual Motor Function; perception (median difference 4, CI 2-17, p=0.014) and Coordination (median difference 7, CI 0-16, p=0.041). Memory problems were seen in 14/37 (38%, MS 10/27 vs non-MS 4/11, p=1.0). Attention problems were reported in 15/37 (41%, MS 10/27 vs non-MS 5/11, p=0.72). Executive function problems were only

detected in 3/37(8%, MS 2/27 vs non-MS 1/11, p=1.0). Duration of disease (>5yrs) or age at disease onset (<12yrs) did not impact the risk of scoring low on the neuropsychological profiles (p=0.08 for both)

Conclusion: Over half the patient in this cohort presented with at least one difficulty in the neuropsychological test. Identification of some subtle difference between the groups are expected in view of the different pathaobiological mechanisms but can also be attributed to the different age at onset. Further correlation with neuroimaging and acquisition of longitudinal neuropsychological analysis are now required to future characterizing the neuropsychological profile of each disease.

S3-P25

Category: Clinical Neuroscience

Cerebral convexity subarachnoid haemorrhage as a transient ischemic attack mimic – a retrospective case-control study

Stanton J[1,2], Wilson D[3], Chandratheva A[2] , Werring, DJ[2,3]

Affiliations: [1]Stroke Medicine MRes Student. [2] University College London Hospitals NHS Foundation Trust [2] Stroke Research Centre, UCL Institute of Neurology.

Background: Non-traumatic (spontaneous) cerebral convexity subarachnoid haemorrhage (cSAH) is a rare, recently-reported transient ischaemic attack (TIA) "mimic"; however, it is often not considered or recognised when a patient presents with transient neurological symptoms. Misdiagnosis of an ischaemic cause for transient neurological symptoms from cSAH may result in inappropriate antithrombotic therapy and an increased risk of future intracerebral haemorrhage.

Aims: To investigate differences in symptomatology between patients with SAH to those presenting to a TIA clinic and identify any markers that may alert clinicians to a haemorrhagic cause of transient neurology.

Methods: A retrospective, case-control study: patients with cSAH, who presented with transient focal neurology were matched (by age and gender) with patients without cSAH presenting to a TIA service. Presenting symptomatology was compared, and the sensitivity and specificity (odds ratio, confidence interval, significance) of any differences was calculated.

Results: Analysis is currently ongoing. It is anticipated there will be different patterns of symptoms or risk factors between patients with cSAH and transient neurology to those without cSAH presenting to a TIA clinic. We hypothesise that haemorrhagic symptoms are more likely to spread anatomically, and more likely to be positive (e.g. paraesthesia) rather than negative (e.g. sensory loss).

Conclusion: We will develop and present an evidence-based tool to triage patients as to having likely cSAH as a source of symptoms. This will be of value in guiding the investigation and management of patients with transient neurological symptoms. This work will raise awareness of this rare TIA mimic amongst clinicians with potential to avoid harm by inappropriate use of antithrombotic drugs.

S3-P26

Category: Clinical Neuroscience

Haplotype analysis and genetic modifiers as predictors of Parkinson's disease penetrance and phenotype severity in G2019S carriers from multi-ethnic populations in the UK

Brown E, Pittman A, Rizig M

Affiliations: Department of Molecular Neuroscience, UCL Institute of Neurology

Background: Mutations in the LRRK2 gene cause a typical late-onset phenotype resembling idiopathic Parkinson's disease (PD). The most prevalent mutation in LRRK2, G2019S, affects ethnic populations differentially; it occurs in 37% of familial North African PD, 23% in Ashkenazi Jewish, and 2.5% in Caucasian cases. Phenotype severity also reportedly varies between ethnicities. The G2019S mutation exhibits incomplete age-related penetrance. Three haplotypes have been identified for pathogenic G2019S, one of which appears to have arisen independently.

Aims: To investigate the effect of pathogenic and non-pathogenic haplotype on disease severity and penetrance, and to identify genetic modifiers of LRRK2 PD.

Methods: Sanger sequencing is being used to identify G2019S mutation carriers from a cohort of 219 PD patients and unaffected relatives. Carriers will subsequently be analysed on a NeuroX array and Illumina Truseq Targeted Neurodegeneration panel. A haplotype tag in DNM3 will be Sanger sequenced to investigate a reported association with age-of-onset modification.

Bioinformatics techniques will be used to analyse haplotypes and identify genome-wide variability affecting phenotype. Clinical data from the MDS-UPDRS and age-of-onset will be utilized.

Results: European G2019S carriers from the preexisting next-generation sequencing data share a common haplotype, with linkage disequilibrium (LD) blocks consistent with northern/western European descent. LD blocks with greater variability in the non-pathogenic allele have also been visualized

S3-P27

Category: Clinical Neuroscience

Clinical and Imaging correlates of Late Onset Depression

Kazmi H[1], Walker Z[2], Booij J[3], Schrag A[1]

Affiliations: [1]Department of Clinical Neuroscience, UCL Institute of Neurology
[2] Psychiatry of the Elderly, UCL Division of Psychiatry
[3] Department of Nuclear Medicine, University of Amsterdam

Background: Late onset depression (LOD) refers to first time depression onset only after the age of 55. The pathology of LOD is complex and unclear, with potentially many factors contributing to the cause of this later life disorder. This study explored the role of dopaminergic function in those with LOD and also the relationship between depression and clinical features associated with later life diseases' such as Parkinson's disease (PD).

Aims: Using brain imaging and clinical assessments to investigate the dopaminergic functioning and any associated clinical features of LOD. To also investigate the relationship between LOD and clinical features associated with PD.
Methods: Participants completed clinical assessments and had 1 DaT SPECT brain scan to measure dopaminergic function in the nigrostriatal pathway.

Results: Preliminary results of clinical measures reveal a higher percentage of LOD patients (N=19) had symptoms associated with early PD such as mild cognitive impairment (57.9% vs 18.2%), REM sleep behavior disorder (42.2% vs 9.1%), olfactory dysfunction (58.1% vs 27.3%), apathy (26.5% vs 9.1%) and subtle motor abnormalities (100% vs 27.3%) in comparison to controls. Depressive symptoms correlated significantly with MDS UPDRS NMS scores (r=.608, p=.006) and MDS UPDRS Total scores (r= .600, p =.007).

Conclusion: These early results indicate the presence of PD symptoms in LOD patients, most notably subtle motor abnormalities. A complete sample set and semi quantitative analysis of the brain imaging together with the clinical measures will increase our understanding of the pathophysiology of LOD and its relationship with early PD.

S3-P27

Category: Electrophysiology

Input specific synaptic integration by hippocampal CA1 parvalbumin expressing fast spiking basket cells

J Cornford, M Mercier, M Liete, V Magloire, DM Kullmann

Institute of Neurology, University College London, Queen Square, London, WC1N 3BG, UK

Parvalbumin-positive (PV^+) interneurons are well-established sources of fast, reliable, and precisely timed feedforward inhibition, for which their biophysics are specialized. In addition, PV^+ interneurons are in a privileged network position as mediators of both feedforward and feedback inhibition. In the CA1 region of the hippocampus, Schaffer collaterals from CA3 can provide the excitatory drive for feedforward inhibition to the PV^+ cells, and synapse mainly on the PV+ cell's dendrites in the stratum radiatium (though also oriens). In contrast, the feedback inhibition drive from local CA1 pyramidal cells is located exclusively on the oriens dendrites.

We show that the dendrites in the oriens, which receive feedback excitation, integrate inputs supra-linearly. In contrast, dendrites in the radiatum integrate inputs linearly. This dendrite dependent non-linear integration is reliant on NMDA receptors, which are not only expressed more strongly by oriens dendrites, but are also more easily recruited by synaptic input due to the specific morphology of oriens dendrites. Using spiking neural network models we show that non-linear input cooperation enables PV^+ cells embedded in winner-take-all networks to distinguish between different input patterns. This finding has implications for the network functions of PV^+ basket cells, such as place cell field regulation.