LND2019

Liverpool Neuroscience Group

Liverpool Neuroscience Day 2019
Poster Abstracts

The role of movement analysis in diagnosing and monitoring neurodegenerative conditions: Insights from gait and postural control

Lisa Alcock[1] , Christopher Buckley[1], Ríona McArdle[1], Rana Zia Ur Rehman[1], Silvia Del Din[1], Claudia Mazzà[2], Alison J. Yarnall[1, 3], Lynn Rochester[1, 3]

1. Institute of Neuroscience, Newcastle University
2. Department of Mechanical Engineering, Sheffield University
3. The Newcastle upon Tyne NHS Foundation Trust

Quantifying gait and postural control adds valuable information that aids in understanding neurological conditions where motor symptoms predominate and cause considerable functional impairment. Disease-specific clinical scales exist; however, they are often susceptible to subjectivity, and can lack sensitivity when identifying subtle gait and postural impairments in prodromal cohorts and longitudinally to document disease progression. Numerous devices are available to objectively quantify a range of measurement outcomes pertaining to gait and postural control; however, efforts are required to standardise and harmonise approaches that are specific to the neurological condition and clinical assessment. Tools are urgently needed that address a number of unmet needs in neurological practice. Namely, these include timely and accurate diagnosis; disease stratification; risk prediction; tracking disease progression; and decision making for intervention optimisation and maximising therapeutic response (such as medication selection, disease staging, and targeted support). Using some recent examples of research across a range of relevant neurological conditions—including Parkinson's disease, ataxia, and dementia— we will illustrate evidence that supports progress against these unmet clinical needs. We summarise the novel 'big data' approaches that utilise data mining and machine learning techniques to improve disease classification and risk prediction, and conclude with recommendations for future direction.

Keywords: Movement science, Parkinson's disease, Dementia, Risk prediction, Disease phenotyping

Dissociation of spatial and non-spatial feature binding in working memory of epilepsy patients with medial temporal lobectomy

Mamdouh Alenazi[1, 2], Mohammad Zia Ul Haq Katshu[3], Haya Aljoudi[1], Faisal Alotaibi[1], Neil Dundon[4], Salah Albaz[1], Tariq Abalkahail[1], Martyn Bracewell[2], Giovanni d'Avossa[2]

1. Department of Neuroscience, King Faisal Specialist Hospital & Research Centre, Riyadh, KSA
2. School of Psychology, Bangor University, Bangor, UK
3. Department of Psychiatry, University of Nottingham, Nottingham, UK
4. University of California Santa Barbara, California, USA

The Medial Temporal lobe (MTL) is a critical structure for episodic and working memory (WM). A prominent theory of MTL function is that the Hippocampus is involved in generating associations between item level representation of previous events, encoded and maintained in Perirhinal Cortex, and their spatial and temporal context, maintained in the Parahippocampal Cortex (PHC) (e.g. Diana, Yonelinas & Ranganath, 2007). An alternative view is that the Hippocampus is involved in feature binding in visual WM, for example, location, shape and colour (e.g. Pertzov et al, 2013). A third suggestion is that spatial binding in WM may take place in the PHC (Dundon et al., 2014). In order to understand the contribution of the MTL to feature binding in visual WM we examined WM performance in a group of patients with TLE who had undergone temporal lobectomy. Patients (n=13) and age-matched healthy controls (n=15) performed two computer-based tasks designed to test WM feature binding and perceptual spatial integration. Performance in the feature WM task was highly heterogenous in the patient group: some patients showed prominent impairment in spatial binding but little impairment in non-spatial binding, some showed impairment in both spatial and non-spatial features binding, but none showed impairments in non-spatial binding only. Patients tended to overweight peripheral over central items in a spatial integration task compared to controls. We conclude that our data support models of MTL which specifically include binding processes that are specifically spatial rather than feature-general.

Keywords: Medial Temporal Lobe, Temporal Lobe Epilepsy, Visual Working Memory, Feature Binding

Analysing developmental effects of materno-foetal thyroid hormone metabolism using mathematical modelling

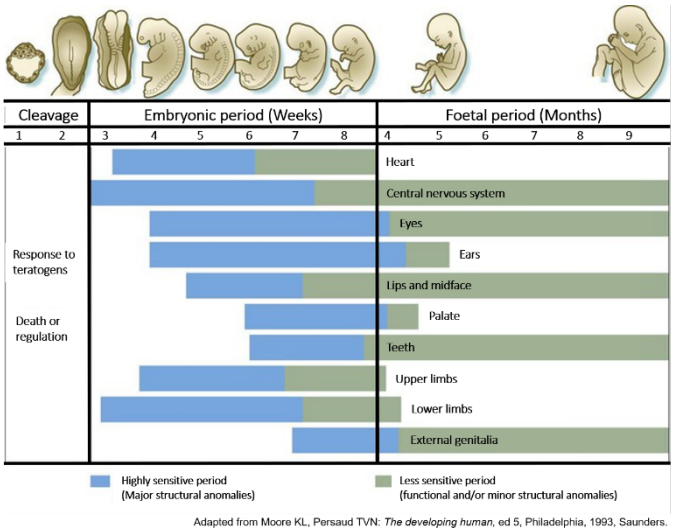
Terence J Allen[1] , Richard A. Currie[2], Louise Dyson[3], Steve Webb[1]

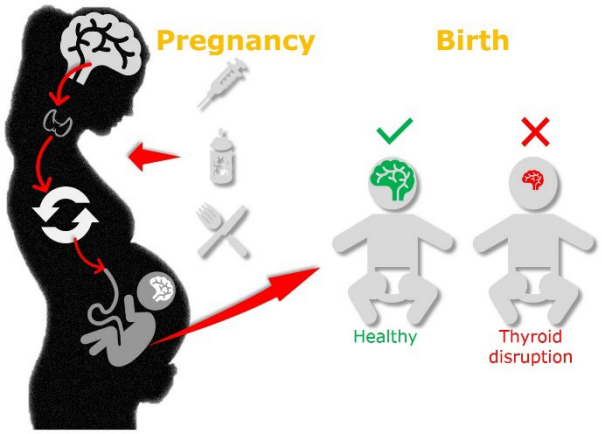
1. Liverpool John Moores University
2. Syngenta UK Ltd
3. Mathemetics Institute, University of Warwick

Thyroid hormones (TH) are essential for the control of metabolism and nervous system development TH essential for growth and development especially for a foetus. In fact, in the first 8 weeks of a development, the foetus is entirely dependent on the mother supplying it with thyroid hormones. These first 8 weeks coincide with periods of high sensitivity for major organs including the CNS. Any perturbation to the mother's TH homeostasis, which is maintained by the Hypothalamic-Pituitary-Thyroid axis, and thus the supply of TH to the foetus in this period could well lead to adverse outcomes in the human foetus.

Exogenous compounds can exert thyroid effects through disruption of homeostasis and thereby TH metabolism dysfunction which can contribute to childhood neurological impairments. Many of these chemicals can cause the induction of Phase II metabolism. This picture becomes more complicated however given that Phase II metabolism involves clearance of the endogenous thyroid hormones triiodothyronine (T3) and its prohormone, thyroxine (T4).

We have developed a multi-compartment model of TH balance in mother and foetus covering key developmental stages of the human foetus when critical neurodevelopmental effects of the TH metabolic network occur, using two mathematical modelling approaches. As well as a physiologically-based pharmacokinetic (PBPK) model which using fully-parameterised ordinary differential equations, we are also pursuing Petri nets as a parallel technique. Petri nets have well defined mathematical foundations that allow characterisation and analysis of concurrent systems such as metabolic networks. Being parameter agnostic, they are concerned solely with network connections, and not the values of the parameters in that network. Thus Petri nets allow quick, initial modelling and can be used to gap-fill missing parameters in the PBPK model.





Keywords: Development, Metabolism, Thyroid, Foetal, Mathematics, Modelling, Toxicology, Pharmacokinetics

Effects of common antiepileptic drugs on biomarkers of oxidative stress in a human neuroblastoma cell line

Reyadh Al-Mosawi[1], Graeme Sills[2, 3]

1. College of Medicine, Babylon University, Iraq
2. University of Liverpool
3. University of Glasgow

Purpose: We have explored the effects of several commonly used antiepileptic drugs (AEDs) on biomarkers of oxidative stress and on the expression of related genes and proteins in a human neuroblastoma cell-line.

Method: SH-SY5Y cells were grown under standard culture conditions. Cells were exposed to carbamazepine (CBZ; 0-100µM), levetiracetam (LEV; 0-300µM), lamotrigine (LTG; 0-100µM) and valproic acid (VPA; 0-1000µM) for 24hrs. Malondialdehyde (MDA) concentration, superoxide dismutase (SOD) activity and reduced/oxidised glutathione (GSH/GSSG) ratio were determined by spectrophotometric assay. Expression of nuclear factor (erythroid-derived2)-like 2 (Nrf2), haemoxygenase-1 (HOX-1) and NADPH quinone oxidoreductase-1 (NQO-1) was determined using real-time PCR and western blot.

Results: MDA concentration was elevated following exposure to CBZ (≤9.5-fold), LEV (≤13.0- fold), LTG (≤25.1-fold) and VPA (≤26.7-fold) (all $p< 0.01$). In contrast, SOD activity was reduced by a factor of up to 7.2 ($p< 0.01$), 2.5 ($p< 0.05$), 5.7 ($p< 0.01$) and 4.0 ($p< 0.05$) after incubation with CBZ, LEV, LTG and VPA, respectively. The GSH/GSSG ratio was also reduced following exposure to CBZ (≤7.8-fold), LEV (≤14.4-fold), LTG (≤10.7-fold) and VPA (≤17-fold) (all $p< 0.01$). Expression of the Nrf2 gene was increased by 75% following exposure to both 100µM CBZ and 1000µM VPA, while expression of HOX-1 was increased by 66% and 63%, respectively (all $p< 0.01$). NQO-1 gene expression was increased after incubation with 100µM LTG and 1000µM VPA by 56% and 52%, respectively (both $p< 0.05$). Relative expression of Nrf2, HOX-1 and NQO-1 proteins was increased by 46% ($p< 0.01$), 26% ($p< 0.05$) and 22% ($p< 0.05$) after exposure to CBZ, LTG and VPA. LEV was without effect on expression of all genes and proteins investigated.

Conclusion: These findings imply that several AEDs have pro-oxidant effects, albeit at high concentrations. This could potentially limit their anticonvulsant activity and/or contribute to their adverse effect profile.

Keywords: Neuroblstoma, Nrf2, GSH/GSSG, Lamotrigine

Brivaracetam add-on therapy for drug-resistant epilepsy: A systematic review and the development of a Patient Decision Aid

Rebecca Bresnahan[1], Mariangela Panebianco[1], Anthony G Marson[1, 2, 3]

1. University of Liverpool
2. The Walton Centre NHS Foundation Trust
3. Liverpool Heath Partners

Approximately 30% of people with epilepsy continue to have seizures despite treatment with an antiepileptic drug (AED). These patients are classified as drug-resistant and require treatment with multiple AEDs. Brivaracetam is a third-generation AED with high-affinity for synaptic vesicle protein 2A.

We conducted a systematic review to evaluate the efficacy and tolerability of add-on brivaracetam for drug-resistant epilepsy.

We searched multiple electronic databases on 9 October 2018 for blinded and unblinded randomised controlled trials with parallel-group design, recruiting people of any age with drug-resistant epilepsy. Two review authors independently assessed trials for inclusion, evaluated trial quality and extracted data. We assessed: ≥ 50% reduction in seizure frequency, seizure freedom, treatment withdrawal for any reason and due to adverse events, and adverse events. We used an intention-to-treat population for all analyses, and presented results as risk ratios (RRs) with 95% confidence intervals (CIs).

The review included six trials (2411 participants). Participants receiving add-on brivaracetam were significantly more likely to attain ≥ 50% reduction in seizure frequency (RR 1.81, 95% CI 1.53 to 2.14) and seizure freedom (RR 5.89, 95% CI 2.30 to 15.13) than those receiving placebo. The incidence of treatment withdrawal for any reason (RR 1.27, 95% CI 0.94 to 1.74), and the proportion of participants experiencing one or more adverse events (RR 1.08, 95% CI 1.00 to 1.17), were not significantly different with add-on brivaracetam versus placebo. Participants receiving brivaracetam were significantly more likely to withdraw from treatment due to adverse events (RR 1.54, 95% CI 1.02 to 2.33).

Add-on brivaracetam for people with drug-resistant epilepsy is effective in reducing seizure frequency and can promote seizure freedom, however, it is associated with increased treatment withdrawal due to adverse events compared with placebo. We are now constructing a patient decision aid to disseminate our findings and support shared decision making.

Keywords: Systematic review, epilepsy, brivaracetam

Bayesian models of expectancy effects on pain perception in chronic pain patients

Eleanor Brian[1] , Nicholas Fallon[1], Andrej Stancak[1], Bernhard Frank[2], Hannah Twiddy[2], Nicola Goodson[3], Nelson Trujillo Barreto[4], Richard Brown[4], Anthony Jones[4], Christopher Brown[1]

1. University of Liverpool
2. The Walton Centre NHS Foundation Trust
3. Aintree University Hospitals NHS Foundation Trust
4. University of Manchester

Chronic pain treatments are only partially successful and almost exclusively symptom-focussed, as the cause of chronic pain remains unknown. Chronic pain almost certainly has some element of central sensitization. For example, patients with fibromyalgia (FM) have widespread chronic pain in the absence of peripheral tissue or nerve damage, while patients with rheumatoid arthritis (RA) can continue to report joint pain despite successful treatment of inflammation.

Pain perception is shaped by experience and expectation, perhaps with associated neuroplasticity contributing to pain and treatment resistance. Bayesian models of perception present a promising approach to understanding how the brain learns and adapts to pain sensing (nociception) over time. Here, we apply this novel approach to understand how the brain learns pain in patients with RA and FM. Our aim is to identify a mathematical model that correctly predicts observed behaviour during nociceptive uncertainty.

In an ongoing study, participants diagnosed with FM and RA are fitted with ring electrodes on the hand and electrical stimulation is given. Following pain threshold testing, patients undergo a behavioural nociceptive learning task where they judge pain intensity in response to electrically-induced digit stimulation. During the task, uncertainty is induced by varying (a) stimulus intensities to increase task difficulty (b) the probability of painful vs. non-painful stimuli. During some blocks, predictive auditory cues are conditioned to the intensity of the painful stimulus with varying probabilities over time, further inducing nociceptive uncertainty.

Results from the first patients will be presented. Bayesian model comparison will identify the best mathematical model that predicts behaviour under nociceptive uncertainty, with initial analyses on pilot data revealing that participants engage in associative learning, perceptual learning and priming to decide whether or not the stimulus is painful. The results will be discussed according to what they suggest about the underlying brain mechanisms affecting chronic pain.

Keywords: Chronic Pain, Bayesian Models, Neuroplasticity

Automatic Subcortical Segmentation of 2D T1-weighted MRI in Epilepsy

Daniel Brownhill[1] , Ya-chin Chen[1], Christine Denby[2], Martyn Bracewell[2, 3], Kumar Das[2], Anthony Marson[2], Simon Keller[1, 2]

1. Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool
2. The Walton Centre NHS Foundation Trust, Liverpool, UK
3. Schools of Medical Sciences and Psychology, Bangor University, Bangor, UK

Background: Numerous techniques exist for automatic segmentation of brain subcortical regions from MRI data; the majority of which, require three-dimensional (3D) MRI scans. MRIs obtained in clinical trials in non-specialist hospitals is typically two-dimensional (2D) meaning use of said techniques has been challenging and not applied, potentially representing a lost opportunity to incorporate volumetric analysis in clinical trial studies. This investigation sought to modify a subcortical segmentation technique developed for 3D MRI scans to apply to and compare with, 2D scans in the same patients with epilepsy.

Methods: 2D (voxel size 0.4x0.4x3mm) and 3D (1x1x1mm) T1-weighted MRI scans were acquired in 31 patients with idiopathic generalised epilepsy. For successful segmentation of the 2D scans, they were re-oriented, cropped and ran through FLIRT for interpolation to a 1x1x1mm resolution. 2D and 3D scans were segmented using FIRST (FMRIB'S Integrated Registration and Segmentation Tool) which automatically identifies the caudate nuclei, globus pallidus, putamen, hippocampus and thalamus. 2D and 3D segmentation volumes were computed using FSL utilities and compared via one-way ANOVA. 2D segmentation reliability was assessed using intraclass correlation coefficients (ICCs) with a threshold level of 0.75, identified as an acceptable level.

Results: Registration failed for 7 of the 2D scans. For the 24 successfully segmented, no significant differences ($P<0.05$) were found in volume in any region between 2D and 3D scans. ICCs for 2D and 3D volumes were above the 0.75 threshold for all regions (mean=0.808).

Discussion: Results suggest an adapted FIRST segmentation can be applied to the majority of 2D scans. Failure in reconstruction of subcortical regions in a minority of 2D scans is under investigation. Volume estimates from successful reconstruction are consistent between 2D and 3D scans. Future work includes applying this technique to MRIs acquired in the SANAD II clinical trial to investigate biomarkers of treatment outcome in epilepsy.

Keywords: Epilepsy, Neuroimaging, MRI, Subcortical region

Diffusional kurtosis imaging of thalamic nuclei as a biomarker of treatment outcome in patients with newly diagnosed focal epilepsy

Lorna Bryant[1], Batil K. Alonazi[2], Yachin Chen[1], James A. Taylor[3], Leonardo Bonilha[3], Emilie McKinnon[3], Jens Jensen[3], Kumar Das[4], Anthony G. Marson[1, 4], Simon S. Keller[1, 4]

1. University of Liverpool
2. Prince Sattam bin Abdulaziz University, Al Kharj, Saudi Arabia
3. Medical University of South Carolina, Charleston, USA
4. The Walton Centre NHS Foundation Trust, Liverpool, UK

Approximately 30-40% of people with epilepsy will continue to experience seizures following anti-epileptic drug (AED) treatment. There are no existing reliable biomarkers of AED treatment outcome. In the present investigation, we used diffusion kurtosis imaging (DKI) to study thalamic microstructure in newly diagnosed focal epilepsy (NDfE), with the aim of identifying biomarkers of AED treatment outcome.

Method: Twenty-seven patients with NDfE and 36 age-matched controls were recruited and underwent DKI scanning and analysis. All patients were followed up one year after neuroimaging to determine response to AED treatment. DKI scalar metric maps were generated using pipelines described in Bonilha et al. (2015) and included mean kurtosis (KMEAN), axial kurtosis (KAX), and radial kurtosis (KRAD). Thalamic nuclei regions of interest (ROIs) were segmented using Freesurfer Segmentation of Thalamic Nuclei and included anterior, intralaminar, pulvinar, medial, lateral geniculate, medial geniculate, ventral anterior, ventral lateral, and ventral postero-lateral. Mean DKI-derived scalar metrics were obtained for each ROI and compared between patients who became seizure free, patients with persistent seizures, and controls.

Results: Sixteen patients continued to experience persistent seizures while 11 patients became seizure free one year after DKI. Patients who experienced persistent seizures had significantly lower KRAD values in the right lateral geniculate (p=.048) and the right ventral postero-lateral (p=.0116) regions of the thalamus compared to patients who became seizure free. No significant differences were found for any other diffusion tensor imaging (DTI-) or DKI-derived metrics.

Discussion: Differences were observed in DKI metrics in patients with persistent seizures compared to seizure free patients. This may be due to changes in the underlying microarchitecture of the thalamus. DKI of the thalamus may be able to provide a non-invasive biomarker for AED treatment outcome.

Keywords: Epilepsy, Neuroimaging, Diffusion Kurtosis Imaging, DKI, DTI, Thalamus, Biomarkers

The Effect of Stimulus Intensity on Rapid Recalibration in Multisensory Integration.

Ketih Colley[1] , Ryan Horsfall[1], Georg Meyer[1], Sophie Wuerger[1]

1. University of Liverpool

Purpose: Simultaneity Judgement (SJ) and Temporal Order Judgement (TOJ) paradigms are used to elucidate the neural mechanisms of Multisensory Integration. It has been demonstrated that stimulus intensity has an effect on multisensory processing by measuring the Temporal Binding Window (TBW) and the Point of Subjective Simultaneity (PSS) (Leone and McCourt, 2015). Furthermore, the PSS has been shown to recalibrate to the leading modality of a single previous trail, this recalibration was due to an adaptation governed by malleable visual leading processing (Van der Burg, Alias and Cass, 2013).

Aim: The current study aimed to investigate the effects of visual stimulus intensity on multisensory integration exploring whether a varying visual stimulus intensity could cause a significant shift in the PSS. If there was a significant effect of intensity on PSS would the effect of stimulus intensity on a current trial recalibrate depended on the relative intensity of a single previous trial.

Methods: 20 participants (10 female, 22-44 years of age) audio-visual stimuli pairs were presented Both the A and V stimuli were 100 milliseconds in duration, with stimulus onset asynchronies (SOAs) of 0, 50±, 100± or 200± milliseconds. Audio leading stimulus were indicated by a negative SOA, while Visual was indicated by a positive SOA. The V stimulus was presented with an interleaved pattern with the intermediate V intensity being presented between the bright and dim intensities.

Results: It was demonstrated in both the SJ and TOJ tasks that in order to be perceived as simultaneous, the visual stimulus had to be presented earlier as the intensity decreased In the SJ task, it was demonstrated that these shifts were governed by the width of the participants TBW. With regards to recalibration, there was no significant recalibration dependent upon the intensity of the previous trial in the SJ or TOJ Tasks.

Keywords: Multisensory Integration, Rapid Recalibration

Changes in brain activation and functional connectivity following prehistoric tool learning

Owen Davies[1] , Georg Meyer[2]

1. University of Liverpool

Human's consistent and complex tool use is distinct from their other primate cousins. It has been posed that learning the skill of flint-knapping a tool via the apprenticeship complexity theory has helped human evolution and the development of the brain. A wide range of structures have been implicated to activate and functionally connect following tool use. Therefore, in this study, the activation across the whole brain, and the functional connectivity between 30 regions of interest were investigated whilst viewing a video of prehistoric tool use and modern tool use. These fMRI sessions occurred both before and after the 14 right-handed undergraduates partook in a flint-knapping training session. As a result, activation was found in a range of structures; the hippocampus, cerebellum, parietal lobe, Broca's area, prefrontal cortex, temporal lobe and motor cortex. Functional connectivity was seen to increase following training between the hippocampus and Broca's area, specifically when viewing prehistoric tool use, and between the parietal lobe, cerebellum and motor cortex, when viewing any tool use, among others. These results suggest that the hippocampus and Broca's area activate in conjunction during recollection of memories of experience gained during flint-knapping. Furthermore, the connectivity increase observed between the cerebellum, parietal lobes and motor cortex may signify a network to address the motor challenges associated with tool use. Ultimately, it seems learning tool manufacture and subsequent use via the apprenticeship complexity theory causes a multitude of activational and functional connectivity changes in the brain, which therefore may have contributed to human brain evolution.

Keywords: Functional Connectivity, Tool use, Learning

Sex differences on the effect of alcohol consumption behaviour and perceived stress on brain activity and executive functioning under stress in young adults, a pilot study.

Rebecca Dwyer[1] , Joanne Ashby[1], Maribel Cordero[1], Elizabeth Walters[2], Halima Mohamud[1], Lucy Walker[1]

1. Manchester Metropolitan University
2. Bradford University

Prolonged stress exposure may be a pathway to alcohol and substance abuse disorders. Evidence suggests that stress and anxiety are linked as causation to alcohol consumption and craving. Young adults may be particularly at risk due to heightened brain vulnerability to alcohol and stress during the development period. Sex differences in the stress response, alcohol tolerance, consumption and subsequent effects on brain function require further examination. The aim of this study was to investigate sex differences on the relationship between alcohol drinking behaviour and stress on prefrontal cortex activity and executive functioning under acute stress in young adults. Twenty-six healthy volunteers between 18 and 30 years of age took part in this study. They completed a range of self-report questionnaires including the General Health Questionnaire (GHQ-28), the Student Health and Lifestyle Questionnaire (SHLSQ) including modified questions on alcohol consumption behaviours and the State-Trait Anxiety Scale (STAI) as well as scales measuring stress levels. Neuropsychological tests were used to measure different aspects of executive function including planning, self-control, and working memory. A stress induction task was implemented to see if this had an impact on performance on the executive functioning tasks.

Brain activity and cognitive performance under stress were assessed and alcohol consumption behaviour, perceived and subjective stress and heart-rate and skin conductance were recorded. It is expected that increased perceived stress will be related to increased alcohol consumption, impaired brain activity and impaired cognitive performance under pressure. Preliminary analyses were conducted. The effects of alcohol consumption and stress exposure on cognitive performance will be analysed and the relationship between brain activity and physiological measures on the effects of stress, alcohol consumption and cognitive performance will be assessed. Full details of the results will be presented throughout the poster.

Keywords: stress, executive function, alcohol consumption, prefrontal cortex

The Neuropathological Effects of Circulating Toxic Bile Acids and Potential Implications in Alzheimer's Disease

Touraj Ehtezazi[1], Andrew G Leach[1]

1. School of Pharmacy & Biomolecular Sicences, Liverpool John Moores University

Recent clinical studies have revealed that the serum levels of toxic hydrophobic bile acids (deoxy cholic acid, lithocholic acid [LCA] and glycoursodeoxycholic acid) are significantly higher in patients with Alzheimer's disease and amnestic mild cognitive impairment when compared to control subjects. The elevated serum bile acids may be the result of hepatic peroxisomal dysfunction.

We have conducted molecular modelling studies to further analyse the neurological damages of LCA. 17 β-estradiol (E2) promotes neurogenesis in dentate gyrus and enhances consolidation of memories and novel object recognition via ERα and ERβ. Our molecular modelling supports that upon binding of LCA with ERα, the helix 12 of ERα cannot cover as a lid over the ligand-binding pocket to secure the ligand in position. Hence, LCA will compete with E2 in binding to ER receptors, but void of physiological actions.

Furthermore, we studied potential interaction between vitamin D and LCA with Aβ 1-40. It has been shown that Vitamin D3-enriched diet correlated with reduced number of amyloid plaques, reduction in Aβ peptides, a decrease in inflammation (reduction of TNF-α in the brain) and increased NGF in the brains of amyloid-β protein precursor transgenic mice. Our molecular modelling work found that LCA could form a complex with Aβ1-40 and compete with the complex formation of Aβ1-40 and vitamin D. Then it may be suggested that LCA would inactivate the neuroprotective effects of vitamin D.

We propose evaluation of serum toxic bile acids levels in patients with Alzheimer's disease, and taking interventions such as the use of cholestyramine or tauroursodeoxycholic acid tablets to lower serum toxic bile acid levels.

Keywords: Alzheimer's disease, dementia, bile acids

Does pre-frontal activation corralate to memory performance in the elderly? An fNIRS study.

Loredana Frau[1] , Deborah Talamonti[1], Davide Bruno[1]

1. Liverpool John Moores University

Background: Older individuals with cognitive deficits have been found to present poor primacy performance and exaggerated recency, in memory tests. However, the recency advantage is usually lost after a delay. In this study, we examined whether the recency ratio (Rr), which encapsulates this memory pattern, and predicts cognitive decline and mild cognitive impairment (Bruno et al., 2016; 2018), is correlated to prefrontal cortex (PFC) haemoglobin levels during resting state, as measured by functional near-infrared stimulation (fNIRS) in healthy older adults.

Methods: 19 participants were tested. All were native English speakers, aged â‰¥65, cognitively intact and with no history of neurological or psychological conditions. 12 channels fNIRS system was used to measure neuronal activities in the PFC at the baseline. To calculate the Rr, we used the List Learning (learning and delayed) subtest of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).

Result: This study shows that Rr is positively correlated to brain haemoglobin levels in the left PFC during rest. These findings support our hypotheses and are consistent with previous neuroimaging studies in which PFC is considered as the neural substrate of retrieval memory.

Conclusion: These results encourage further exploration of the fNIRS connectivity to explain cognitive functioning and its potential application for the analysis of hemispheric relationships within the serial position effect. Future research may consider the Rr as emerging cognitive variable in the neuropsychological assessment to detect age memory loss in the elderly.

Keywords: fNIRS, prefrontal cortex, memory, cognitive aging

Towards a framework of coping following severe traumatic brain injury

Lydia Holland[1] , Eleanor Whittaker[1], Joanne Powell[1]

1. Edge Hill University

Background and rationale: This study was informed by the current paucity of research investigating Traumatic Brain Injury (TBI) and the coping mechanisms adopted following the event. Investigations into health-related quality of life (HR-QOL) within populations, such as those with diabetes and heart disease, have revealed the widespread impact such conditions can have on physical and mental wellbeing. However, HR-QOL has not been investigated within a TBI sample. Adopting positive coping mechanisms following a TBI has been identified as important in maximising recovery outcomes and HR-QOL.

Aims: This study will investigate HR-QOL outcomes in severe TBI survivors, in particular, how survivors' post-injury experiences and challenges inform positive and negative coping styles and how these coping styles impact perceived QOL will be explored.

Method: Semi-structured interviews were conducted with five survivors of severe TBI's. Participants were between 3-to-10 years post-injury. Interviews were transcribed verbatim and analysed using grounded theory.

Results/ Findings: The data informed the development of the TBI model of coping, following the identification of five codes that informed the adoption of successful coping strategies: (1) Support and Understanding, (2) Purpose, (3) Management, (4) Coping, and (5) Acceptance. The TBI model of coping highlights that adequate satisfaction of all five codes increases the likelihood of positive coping style adoption such as problem- focused coping and better perceived QOL.

Conclusions: This study is the first to investigate the relationship between coping style and HR-QOL in a severe TBI sample. Future research directions that may further elucidate the TBI model of coping's five components are suggested.

Keywords: neuro rehabilitation, traumatic brain injury, quality of life, coping

Is Attachment Anxiety a Useful Measure of Adult Social Development?

Emily Jackson[1]

1. Liverpool John Moores University

Background: Touch is fundamental for our well-being, emotional resilience, social development, and relationships throughout the lifespan. Research shows that childhood maltreatment is related to a higher incidence of insecure attachment and autism. In addition, touch avoidance behaviors characteristic of autism and attachment insecurity are parallel.

Aims: To explore the relationship between level of anxious and avoidant attachment, autistic characteristics, and subjective attitudes towards pleasant touch.

Sample: Seventy-nine participants were used in the current study. Three had significant autistic traits, scoring above 32 on the AQ.

Method: Three self-report questionnaires measuring attachment avoidance/anxiety; positive personal touch experiences; and degree of autistic traits were completed.

Results: A two-way independent MANOVA assessed the effects of attachment style on number of autistic traits and attitudes towards affective touch. Findings are in line with previous research, displaying that insecure avoidant (but not anxious) attachment is significantly associated with reduced touch seeking ($F(1, 75) = 15.37$, $p = .000$, $\eta p2 = .17$). Findings also suggest that only attachment avoidance is significantly associated with number of autistic traits, specifically diminished communication ($F(1, 75) = 8.33$, $p = .005$, $\eta p2 = .10$).

Conclusions: Touch experiences and number of autistic traits are influenced by attachment avoidance but not anxiety. This calls into question whether attachment anxiety is a valid classification. Future research should explore the mechanisms behind avoidant attachment and autism, to establish if they are underpinned by the same developmental flaw, possibly in the C-tactile system.

Keywords: C-tactile, Affective, Development, Attachment, Autism, Avoidance, Anxiety.

Finding treatments for drug resistant epilepsy: Identification of novel anticonvulsant compounds using diverse model organisms.

Alistair Jones[1] , M. Herd[3], V. Cunliffe[2], M. Barker-Haliski[4], S. White[4], T. Marson[1], G. Sills[1], A. Morgan[1]

1. University of Liverpool
2. University of Sheffield
3. University of Dundee
4. University of Washington (Seattle)

Despite epilepsy being one of the most common neurological disorders one-third of patients remain without effective anticonvulsant treatments. Unfortunately, anticonvulsant discovery remains static. The lack of drug-discovery can be partly attributed to species-specific effects and bottle-necks during in-vivo rodent testing. By utilising the high-throughput models C. elegans (nematode worm) and D. rerio (Zebrafish) as front-line screening tools, larger scale compound testing is feasible, and species-specific effects would be reduced; increasing the translational potential of positive compounds. This approach was validated through the compound LIV001 identified in a D. rerio screen of 2000 compounds utilising c-fos expression in response to the pro-convulsant pentylenetetrazol (PTZ). LIV001 pre-treatment significantly reduced PTZ induced convulsive phenotypes in both D. rerio and in C. elegans ($p>0.05$). A molecular target was identified using a C. elegans genetic screen against a LIV001induced paralysis phenotype. Here, worms with mutant lgc-37 (a GABAA receptor subunit orthologue) were significantly resistant to the compound $p>0.05$. Paralysis resistance in these mutants was reversed through reintroducing the native lgc-37 gene and, in wild type worms, pharmacological antagonism of the GABAA channel protected against LIV001-induced paralysis. This GABAA mechanism was conserved in mouse thalamocortical relay neurons, as demonstrated by LIV001's stimulatory effect on both tonic (LIV001 tonic current 589±157pA vs -324±111pA control) and phasic inhibition (LIV001 mIPSC peak amplitude -51.1± 3.1 vs -43.3± 2.2). LIV001 was shown to be anticonvulsant in a battery of mouse acute seizure tests. Notably, efficacy was demonstrated in the 6Hz 44mA assay of pharmacoresistant seizures, protective index (PI) 2.3 (PI=median toxic dose/median effective dose), distinguishing LIV001 from several FDA approved anti-convulsants (ED50=66.2mg/kg, CI=45.8-102). We describe here conserved anti-convulsive effects in all three models, rapid characterisation of molecular targets and identification of a compound effective in a mammalian pharmacoresistant seizure model using our pipeline, highlighting the benefits of this approach.

Keywords: Epilepsy, Seizure, Zebrafish, C. elegans, Pharmacology, Drug-discovery

MRI volumetry reveals thalamic atrophy in patients with newly diagnosed focal epilepsy

Nicola Leek[1] , Mollie Neason[1], Besa Ziso[3], Samia Elkommos[4], Graeme Sills[1], Kumar Das[3], Tony Marson[1], Andrea Jorgensen[2], Simon Keller[1]

1. Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool
2. Department of Biostatistics, Institute of Translational Medicine, University of Liverpool, UK
3. The Walton Centre NHS Foundation Trust, Liverpool, UK
4. St George's University Hospitals NHS Foundation Trust, London, UK

Background: Imaging studies of newly diagnosed epilepsy (NDE) provide important information about epilepsy diagnosis and treatment. Patients are rarely studied from the point of diagnosis, despite this being a crucial time point in understanding the underlying neurobiology of epilepsy. Approximately 30-40% of adults diagnosed with NDE never achieve seizure freedom. However, there are no current imaging biomarkers of treatment outcome. The purpose of this study was to determine whether volumes of subcortical structures that have been demonstrated to be important in refractory epilepsy are atrophied in patients with newly diagnosed focal epilepsy (NDFE), and whether volume alterations are related to clinical aspects of the disorder.

Methods: A total of 82 patients with NDFE and 40 healthy controls received a T1-coronal FLAIR MRI scan. Volume estimation of the left and right hippocampus, thalamus, putamen, caudate nucleus and temporal lobe were performed using stereology in conjunction with point counting on MRIs for all participants. Subcortical volumes were normalised using whole brain volume. Clinical data was obtained for patients, including age of first seizure, duration of illness, seizure remission, therapy type and EEG finding.

Results: Normalised left thalamic (U=878, p=0.000), hippocampal (U=1068, p=0.002) and temporal lobe (U=1057, p=0.001) volume was significantly smaller in patients relative to controls. Right thalamic (U=1127, p=0.005) and hippocampal (U=1208, p=0.018) volumes were also smaller in patients before Bonferroni correction. In patients, a decrease of 7.5% was observed in the left thalamus, 9.3% in the left hippocampus and 5.5% in the left temporal lobe. Individual volumetric analysis found fourteen (17.1%) patients had abnormal left thalamic volume, and nine (11.0%) patients had abnormal left hippocampal volume, only two (2.4%) patients had abnormal temporal lobe volume. Thalamic atrophy was not associated with any clinical variables.

Significance: This study reports the first evidence for thalamic atrophy in NDFE. The cause of volume loss in brain structures in NDFE is unclear and likely not due to seizure severity or antiepileptic medication.

Keywords: Epilepsy, MRI, Neuroimaging, Newly diagnosed epilepsy, thalamus

Network changes in patients with idiopathic generalised epilepsy analysed using Network Based Statistics (NBS)

Andrea McKavanagh[1], Barbara A. Kreilkamp[1], Christine Denby[2], Martyn Bracewell[2, 3], Kumar Das[2], Anthony G. Marson[1, 2], Peter Taylor[4], Simon Keller[1, 2]

1. Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool
2. The Walton Centre NHS Foundation Trust, Liverpool, UK
3. Schools of Medical Sciences and Psychology, Bangor University, Bangor, UK
4. Interdisciplinary Computing and Complex BioSystems Group, School of Computing Science and Institute of Neuroscience, Faculty of Medical Science, Newcastle University, UK

Idiopathic generalised epilepsy (IGE) is a collection of genetically based non-lesional epileptic disorders which account for one third of all epilepsies. Around 30% of patients with IGE are refractory to drug treatment and continue to have debilitating seizures. The mechanisms underlying persistent seizures after drug treatment are not well understood, and there are currently no reliable biomarkers to predict treatment outcome in individual patients. Brain imaging offers unparalleled opportunities for the development of in-vivo non-invasive biomarkers in brain disorders. Epilepsy is a network disorder; sophisticated MRI techniques can be used to model brain networks. The objectives of this work were to characterise brain structural network alterations in patients with IGE using NBS applied to diffusion tensor imaging (DTI) data, and to determine whether brain network alterations were different between patients with well-controlled and poorly-controlled seizures.

Thirty five patients with IGE (11 seizure free and 24 persistent seizures) and 40 age and sex-matched healthy controls were recruited. Structural connectivity networks were built from T1-weighted and DTI data; 82 cortical and subcortical nodes were segmented from T1-weighted images using Freesurfer software. Connecting edges between nodes were reconstructed using the DTI data. Network differences in mean diffusivity, radial diffusivity, fractional anisotropy and count between IGE seizure free, IGE persistent seizures and control groups were compared using NBS.

Statistically significant bilateral network changes were observed between patients and controls. All patients had decreased fractional anisotropy and count across both cerebral hemispheres compared to controls. Patients with persistent seizures had additional mean diffusivity and radial diffusivity based network alterations relative to patients rendered seizure free and controls.

Although a non-lesional disorder, network analysis revealed bi-hemispheric structural network alterations in patients with IGE, which may provide insight into the mechanisms of the disorder. Given that particular network alterations were unique to patients with persistent seizures, network analysis may be useful for identifying imaging biomarkers of refractory IGE.

Keywords: Epilepsy, IGE, MRI, Networks, Seizure freedom, Treatment outcome

Characterisation and regulation of the SVA retrotransposable elements within the Parkinson's disease associated locus INPP5F/BAG3

Ben Middlehurst[1] , Sulev Kõks[2], Vivien J. Bubb[1], John P. Quinn[1]

1. University of Liverpool
2. Perron Institute for Neurological and Translational Science

Understanding the fundamental regulation of Parkinson's disease-related genes is key to understanding the aetiology of the disease given the absence of causation inferred from current genome wide association studies (GWAS). One explanation for the lack of causative mutations inferred from GWAS data could be that the mutations/polymorphisms implicated in the disease are not catalogued in short read sequencing data as they may originate in retrotransposable DNA such as SVA's (~2kb hominid specific domains). These elements are often excluded from such analysis due to their highly repetitive nature which leads to imputation issues. To test this, genotyping of polymorphic variants in an SVA F element within the GWAS identified risk loci INPP5F/BAG3, was performed in a cohort containing 149 Parkinson disease case and 175 matched control DNA samples. BAG3 has previously been reported in the progression of PD, independently of GWAS, via the implication in alpha-synuclein aggregation pathways leading to pathology. Polymorphic domains were identified in the SVA F element, with no statistical association of variation being reported between case and control in this preliminary study with relatively small N numbers. To assess if SVA's have potential regulatory effects, we have used modern molecular biology techniques including CRISPR and luciferase-based reporter gene assays within established mammalian cell lines and human iPSC cell lines including forebrain cortical neuron derivations. We have demonstrated that SVA retrotransposons within the INPP5F loci show significant repressive regulatory effects in a reporter gene assay in both established cell lines and iPSC models which may be differential between cell types. Further validation and testing is currently being performed using CRISPR to knockout the SVAs of interest and test their effect on gene expression, differential isoform expression and ability to respond to stimulus, such as the transcription factors CTCF or BORIS, which have been reported to bind to SVAs.

Keywords: Genetics, Retrotransposons, Parkinson's disease

Autoimmune encephalitis as an increasingly recognised cause of non-convulsive status epilepticus

James Mitchell[1, 3], Sofia R. de Valdoleiros[1, 4], Benedict Michael[1, 2]

1. The Walton Centre NHS Foundation Trust
2. Institute of Infection and Global Health, University of Liverpool
3. Institute of Translational Medicine, University of Liverpool
4. Institute of Translational Medicine, University of Liverpool

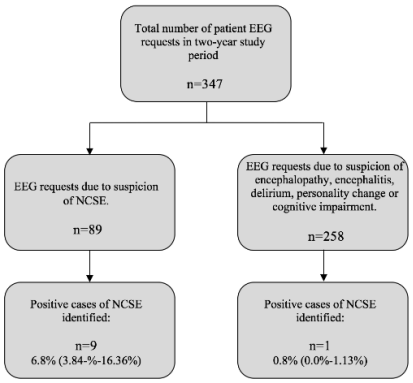
Introduction: Non-convulsive status epilepticus (NCSE) can be difficult to diagnose as patients present with confusion or personality change with minimal signs on examination that there is ongoing seizure activity. The diagnosis of NCSE is critically dependent on the results of electroencephalography (EEG). There is currently little evidence pertaining to the typical clinical characteristics, diagnosis and management of patients diagnosed with NCSE in the UK.

Aim and methods: This study aimed to describe a case series of patients diagnosed with NCSE in a large neurophysiology department covering a regional neurology referral center as well as three secondary care facilities for general medical and surgical patients over a three-year period. EEG data and case notes from consecutive EEG requests were reviewed between January 2015 and December 2018 to identify demographic, clinical, treatment and outcome data.

Results and discussion: In total, 347 EEGs were requested due to a clinical suspicion of NCSE, behavioural change or impaired consciousness. Ten cases of patients in NCSE were identified from this cohort, with 6.8% (95% CI 3.84%-16.36) of EEGs performed on patients with clinical suspicion of NCSE consistent with this diagnosis. As outlined in previous literature, epilepsy, encephalitis and meningitis were common comorbidities. The most frequent presenting clinical feature was reduced level of consciousness (70.0%, 95%CI 41.6%-98.4%). Myoclonus or subtle motor signs were observed in 50.0% of the cohort (95%CI 19.0%-90.0%). NCSE was attributed to presentation of previously diagnosed epilepsy in three patients, and interestingly secondary to autoimmune encephalitis in three other patients.

Conclusion: Autoimmune encephalitis is being increasingly recognised cause of NCSE, and should be considered in patients with suspected encephalitis with acute onset behavioural changes, reduced level of consciousness, myoclonus or subtle motor signs.

Figure 1. Proportion of cases with NCSE on EEG



NCSE; non-convulsive status epilepticus, EEG; electroencephalogram. 95% confidence intervals for proportions presented in parentheses.

Figure 2. Demographic and clinical characteristics

Case series		Years (IQR)
Median age, yrs (IQR)		58.5 (45.8-65.5)
	Frequency, n=10	**Proportion, % (95% CI)**
Male	5	50.0% (19.0%-90.0%)
Co-morbidity:		
Epilepsy	4	40.0% (9.6%-70.4%)
Previous encephalitis	1	10.0% (0.0%-28.6%)
Previous meningitis	1	10.0% (0.0%-28.6%)
Alcohol excess	4	40.0% (9.6%-70.4%)
Previous neurosurgical procedure	1	10.0% (0.0%-28.6%)
Presenting clinical features		
Reduced conscious level	7	70.0% (41.6%-98.4%)
Myoclonus / other subtle motor signs	5	50.0% (19.0%-90.0%)
Acute confusional state	3	30.0% (1.6%-58.4%)
Behavioural disturbance	3	30.0% (1.6%-58.4%)
Diagnosis		
NCSE as presentation of previously diagnosed epilepsy	3	30.0% (1.6%-58.4%)
NCSE secondary to autoimmune encephalitis	3	30.0% (1.6%-58.4%)
NCSE secondary to acute ischaemic stroke	1	18.6% (0.0%-28.6%)
NCSE secondary to hypoxic brain injury	1	18.6% (0.0%-28.6%)
NCSE secondary to traumatic brain injury	1	18.6% (0.0%-28.6%)
NCSE secondary to CNS vasculitis	1	18.6% (0.0%-28.6%)

Keywords: NCSE, Epilepsy, EEG, Autoimmune encephalitis

The Study of Radiomics in Glioblastoma Multiforme

Lauren Moreton[1]

1. University of Liverpool

Glioblastoma Multiforme (GBM) describes a heterogeneous tumour that has arisen from star-shaped glial cells in the central nervous system. Prognosis of individuals with GBM is poor, with the average median survival time being 12.6 months from diagnosis. Primarily, imaging tests followed by histomorphological analysis of tumour samples is used to identify the phenotype of tumours, which influences prognosis and construction of treatment plans. However, this invasive method can be costly and time-consuming. To overcome this, we propose the use of a computer-based machine-learning radiomics model to identify genetic tumour characteristics through the texture analysis of medical images. Radiomics is a high-throughput computerised workflow that employs machine learning strategies to provide links between tumour heterogeneity and biomarker characteristics. Although attempted before, previous studies have failed to assess the issue of reproducibility and standardisation. Poor reporting and small sample size had led to cases of â€˜overfitting the data' reducing the robustness and reliability of results. To combat this, we analysed 335 MRI images strictly adhering to the Imaging Biomarker Standardisation Initiative (IBSI) with the aim of setting a benchmark for a standardised radiomics workflow in order to achieve valid texture analysis which can be transposed into the clinic. Using PyRadiomics software, we were able to extract texture features from 303 3D T 1 Contrast Scans of patients with GBM, studying global brain changes as well as intra-tumour heterogeneity. Future work comprises the implementation of machine learning methods using clinical data in order to derive biomarker characteristics in gliomas. This would lead to the production of a predictive and prognostic tool that could be used to augment existing diagnostic techniques, potentially increasing accuracy in smaller time constraints.

Keywords: Glioblastoma Multiforme, Radiomics, Texture Analysis

Assess the viability and intracranial biodistribution of human embryonic stem cell-derived dopaminergic progenitors in rats using non-invasive imaging techniques

Masoumeh Mousavinejad[1] , Chris Hill[1], Arthur Taylor[1], Patricia Murray[1]

1. Department of Cellular and Molecular Physiology, Institute of Translational Medicine, University of Liverpool

Human embryonic stem cells (hESCs) and induced pluripotent stem cells are powerful tools with great potential for modelling and treating neurodegenerative diseases as they are able to differentiate into neuronal and glial cell linages in response to appropriate signals. Parkinson disease (PD) is one of the most common neurodegenerative disorders affecting older people, which is characterized by degeneration of dopaminergic neurons in the substantia nigra which leads to tremor, muscle rigidity and instability in movement. The ineffectiveness of current medications for PD has motivated development of cell-based treatment approaches to offer a new way to replace the neurons lost due to the disease, thereby restoring the dopamine levels in the patient's brain permanently. A current challenge, however, is to track transplanted cells and determine their contribution to functional recovery. In the present study we use imaging reporters (luciferase and iron oxide) for non-invasive imaging (Bioluminescence, BLI, and Magnetic Resonance Imaging, MRI) to analysis and determine the viability, biodistribution, and tumourigenic potential of transplanted Ventral Midbrain (VM) progenitors derived from hESCs. A bicistronic lucifrase-ZsGreen hESC reporter line was first established, which was differentiated into VM progenitors for assessing and tracking cells using BLI in vivo. To monitor the intracranial biodistribution of the cells with MRI, a proportion of administered VM progenitors were labelled using micron size iron oxide particles that were labelled with a red fluorophore. Cells were administrated into the striatum of the rat brain and imaging was performed every two weeks. The preliminarily results show that the engrafted-labelled VM progenitors formed neurons that expressed the dopaminergic neuron-specific marker, tyrosine hydroxylase (TH), suggesting that the labelling technique did not negatively impact on the ability of the VM progenitors to mature and differentiation into TH+ neurons in vivo. Moreover, BLI and MRI showed no evidence for tumour formation post implantation, suggesting that the progenitors are not tumourigenic, irrespective of whether they express a genetic reporter, or are labelled with iron oxide particles.

Keywords: Stem cells, Parkinson, Bioluminescence, Magnetic Resonance Imaging

A longitudinal investigation of the neurodevelopmental impact of Maternal Immune Activation on parvalbumin interneurons in the Prefrontal Cortex and Dorsal Hippocampus in the rat.

Syeda Munni[1] , Ben Grayson[1], Giovanni Podda[1], Zing Yeo[1], Vicki Fasolino[1], Joanna Neill[1], Michael Harte[1]

1. The University of Manchester

Introduction: Prenatal environment affects the developing fetus (Knuesel et al, 2014, Nat Rev Neurol, 10:643-660). Maternal immune activation (mIA) in rodents by administration of a viral mimetic polyriboinosonic-polyribocytidylic (poly I:C) is used to study effects of prenatal infection on offspring neurodevelopment. Our aim is to investigate the longitudinal development of PV deficits and to determine whether cognitive deficits and PV reductions in the offspring occur at the same stage of development.

Methods: Pregnant Wistar rats from two cohorts (c1 & c2) were injected i.p with poly I:C (10 mg/kg, n=14) or vehicle (n=11) on gestational day (GD) 15. Body weight (BW) and core body temperature (CBT) were recorded at the first 24h. Blood taken 3h post-injection to measure IL-6. Pups from c1 were culled at different time points- PND35 and PND70 to create a PV expression timeline in this model. Female offspring (c2) culled at PND 130. PV levels were analysed (c1 & c2) in the prefrontal cortex (PFC) and dorsal hippocampus (DHC) using Western Blotting (WB). Data analysed by univariate GLM.

Results: Poly I:C significantly increased IL-6 at 3h compared to vehicle ($p<0.05$). A significant decrease in BW ($p<0.05$) but not CBT in the first 24h (c1 & c2) was observed. WB analysis showed no changes in PV in PFC or DHC at PND35 or PND70 in both sexes (c1). However, significant decrease ($p<0.05$) in PV in the PFC at PND130 in female offspring was observed (c2).

Conclusion: No changes in PFC PV at PND35 or PND70 but a significant decrease in female offspring in adulthood, suggesting co-occurrence between the timing of behavioural deficits and reduced PV in the PFC. This supports the hypothesis that PV deficits are a mechanism for cognitive dysfunction in this model although further studies are required to understand the origin of the reduced PV.

Keywords: Maternal immune activation, prenatal infection, neurodevelopment

Suitability of CNS Active Drugs for a Genome Wide Genetic Screen

Daniel Seddon[1]

1. University of Liverpool

Central nervous system (CNS) drug developers continually ignore the need for a defined route across the blood-brain barrier (BBB) with many marketed CNS drugs having uncharacterised uptake. However, a genome wide genetic screening approach has been developed with the potential to identify any drugs uptake transporter if it exists. The screen facilitates random loss of function mutations in a haploid cell population. Mutated cells that survive exposure to a cytotoxic drug dose can be analysed to determine the transporter gene knockout responsible for resistance. The psychoactive compounds cocaine, oxycodone and fentanyl, the anti-psychotic clozapine and anti-epileptic carbamazepine, are all suggested to undergo carrier-mediated uptake at the BBB. To examine a potential overlap in the transport of these compounds before use in the screen, trans-stimulation of [H3]-clozapine was investigated in human cerebral brain capillary endothelial (hCME3/D3) cells. Clozapine, oxycodone, fentanyl and cocaine all stimulated [H3]-clozapine transport suggesting an antiporter is responsible for transport of all 4 compounds, whereas carbamazepine had no effect suggesting use of a separate transporter. Each compound was also assessed for cytotoxicity by a 3-day ATP and 7-day colony formation assay. Results from both assays show each drug to be sufficiently cytotoxic for inclusion in future iterations of the genome wide genetic screening approach with carbamazepine being the most cytotoxic (IC50 = 0.317mM).

Keywords: Blood Brain Barrier, Drug Transporters, Drug Uptake, Psychoactive, Genetic Screening,

Investigation of the novel drug Sep-363856 in the phencyclidine model of schizophrenia

Federica Sensini[1, 2] , V. Begni[1], M. Burgess[2], B. Grayson[2], S. Munni[2], J. Neill[1], M. Riva[1], A. Sanson

1. Division of Pharmacy and Optometry, University of Manchester
2. Manchester Pharmacy School, University of Manchester

Background: Dysfunction in certain neurotransmitter pathways has been shown to mediate the pathophysiology of schizophrenia, particularly N-methyl-D-aspartate receptor (NMDA-R) hypofunction. Accordingly, administration of NMDA receptor antagonists such as phencyclidine (PCP) is now used as an experimental model to investigate symptomatology of schizophrenia. SEP-363856 (SEP) is a new drug that interacts with both 5-hydroxy-tryptamine 1A (5HT1A) and trace-ammine associate receptor 1 (TAAR1) receptors, providing a novel therapeutic for schizophrenia. The aim of this study was to evaluate the ability of SEP in comparison to the atypical antipsychotic risperidone (risp) to prevent molecular and behavioural responses induced by PCP.

Methods: A total of 60 adult female Lister Hooded rats (233g ±22g) were pre-treated with SEP (1, 3 and 10 mg/kg, p.o.), risp (0.1 mg/kg, i.p.) or vehicle and placed immediately into individual locomotor activity-LMA- chambers (PAS version 2.0) for 60 min. Rats subsequently received a second injection of vehicle or PCP (2 mg/kg, i.p.) and were immediately returned to the LMA apparatus for a period of 90 min and then sacrificed. Real time PCR of immediate-early genes (IEGs) and Bdnf were performed on selected brain regions.

Results: The results showed that acute treatment with PCP significantly increased LMA, whilst administration of SEP at all doses and risp prevented the PCP-induced hyperactivity response. Molecular analyses revealed that n PCP upregulated mRNA levels of IEGs (Arc, Zif268, c-fos and Npas4) as well as of Bdnf in prefrontal cortex (PFC) and downregulated the same genes in hippocampus and striatum. These changes were prevented by both SEP and risp in PFC, whereas only risperidone was effective in the ventral hippocampus. Neither SEP nor risp prevented downregulation in dorsal hippocampus and striatum.

Conclusions: The data show that SEP prevented the behavioural and molecular effects, particularly in PFC, induced by glutamate-receptor hypofunction following acute treatment with PCP.

Keywords: schizophrenia, PCP, behavioral

A Diffusion Tensor Imaging investigation into potential white matter alterations in the microstructure of the fornix in the early stages of Parkinson's Disease

Hilary Shepherd[1], Simon Keller[1], Barbara Kreilkamp[1]

1. University of Liverpool

Parkinson's Disease (PD) has several non-motor symptoms that severely impact patients' lives. Cognitive impairment is one common non-motor symptom that leads to a range of psychiatric and behavioural issues in the later stages. Recent studies suggest, however, approximately 25%-40% of patients will be affected by cognitive impairment in the early stages of PD. Diffusion Tensor imaging (DTI) is a technique widely used to assess the integrity of White Matter (WM) structures and offers the potential to be a non-invasive, diagnostic biomarker that reflects cognitive impairment. In this study DTI was used to reconstruct and assess the integrity of the fornix, a WM tract bundle important to memory. T1-weighted magnetic resonance images (MRI), DTI scans and clinical data were obtained from the Parkinson's progression marker's initiative (PPMI) online database, for 20 patients with PD and 20 age and sex matched controls. Fornix reconstruction and Fractional Anisotropy (FA) measurements, used to assess WM integrity, were carried out manually in TrackVis software. FA measurements were also correlated against age and memory scores. No statistically significant differences were found between FA values measured in patients and controls. One significant result ($p<0.05$) found was for increased right fornix FA and increased performance in the Hopkins Verbal Language test. However, all other correlations conducted between FA and memory scores/age were found to be not statistically significant. A negative correlation was also found between FA value and increase in age however, this was also found to not be statistically significant ($p>0.05$).

Keywords: Parkinson's, Early stage, Biomarker, Cognitive impairment, DTI, Fornix, FA

Understanding the link between oxidative stress, microtubule aberrations and neuronal ageing

Samuel Shields[1] , Ian Prior[1], Natalia Sanchez-Soriano[1]

1. Institute of Translational Medicine, University of Liverpool

Oxidative stress is described as an imbalance in the production and detoxification of reactive oxygen species (ROS) and, for decades, has been strongly linked with ageing and age-related neuropathologies such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis (ALS). Many ROS are now considered important cellular messengers due to their capacity to reversibly alter protein function and localisation through the oxidation of exposed thiol groups. Therefore, current hypotheses within the field of ageing view the causal link as the downstream perturbations in redox-regulated signalling pathways - opposed to the traditional macromolecular damage theory. Our research focus is directed towards how microtubule deregulation contributes to age-related neuronal decay. Studies investigating disease, primarily ALS, have begun to unveil the link between microtubules and ROS, although, with very limited mechanistic understanding. We intend to utilise Drosophila melanogaster as a model of ageing and neuronal physiology to investigate how conditions of oxidative stress impact microtubule function and characteristics. Here we show that SOD1 mutants and treatment with the redox-cycler paraquat disrupts microtubule organisation within neurites in vitro and that (co)administration with the vitamin E analogue trolox, or knockdown of the NRF2 inhibitor Keap1 is capable of rescuing the disorganisation phenotype. Furthermore, a significant reduction in EB1 (end binding protein) profile at polymerising ends of microtubules, indicative of destabilised microtubules, was apparent in both conditions. Finally, within our novel in vivo ageing brain model, we report a reduction in axonal swellings, microtubule disorganisation and terminal microtubule fragmentation (apparent in aged flies) in Keap1-knockdown flies. From our data we demonstrate that conditions of oxidative stress modulate neuron microtubule bundling which may occur through direct or indirect regulation of the MAP EB1. Furthermore, that manipulation of the antioxidant master regulator NRF2, is capable of reducing detrimental age-associated microtubule phenotypes in vitro and vivo.

Keywords: Oxidative Stress, Redox, Microtubules, Cytoskeletal, Ageing, Neurodegeneration, Drosophila melanogaster, Fly

Synaptic biomarker reduction and impaired cognition in the sub-chronic PCP mouse model for schizophrenia

Rebecca Smausz[1], John Gigg[1], Francesca Mcewan[1], Michael Harte[1], Joanna Neill[1]

1. The University of Manchester

Lack of effective treatments for cognitive deficit and negative symptoms of schizophrenia calls for the development of validated, translational animal models and appropriate tests. Sub-chronic phencyclidine (scPCP) administration has provided a translational rat model, but a mouse model is currently not well characterized. However, the higher potential for genetic manipulation of mice provides certain advantages, given the genetic aetiology of schizophrenia. The present study investigated the effect of scPCP on object recognition memory and synaptic biomarkers. Sixteen female C57BL/6 mice received either once daily 10mg/kg subcutaneous PCP or vehicle injections (n=8/group), for ten consecutive days. Novel Object Recognition (NOR) memory was tested in a Y maze, while the effect of distraction was investigated by either moving the mice to a holding cage or keeping them in the arena during the inter-trial interval. Post-mortem analysis of parvalbumin (PV), postsynaptic density 95 (PSD95), glutamic acid decarboxylase (GAD67) and synaptosomal-associated protein 25 (SNAP25) levels was subsequently performed in the frontal cortex and dorsal and ventral hippocampus. scPCP mice showed marked NOR deficits when distracted by removal from the arena, treating previously encountered objects as novel at test. Decreased PV levels in all studied areas and lower PSD95 expression in the frontal cortex and ventral hippocampus were found in scPCP mice, with no changes in GAD67 and SNAP25 levels. These findings provide evidence for the validity of the scPCP mouse model for studying schizophrenia, as rodent NOR deficits and susceptibility to distraction correlate well with declarative memory impairments and poor concentration in patients, while synaptic marker reductions have been reported in equivalent human brain regions. Thus, the scPCP mouse model will be very useful for developing improved treatments for currently untreated symptomatology in certain schizophrenia patients, providing the advantage of potential for genetic manipulation.

Keywords: Mouse, Schizophrenia, Phencyclidine, Parvalbumin, PSD95, Novel Object Recognition

Investigating the role of serotonin signalling in Hirschsprung's disease.

Megan Smith[1], Sumita Chhabra[1, 2], Bettina Wilm[1], Patricia Murray[1], Simon Kenny[1, 2], David Edgar[1]

1. University of Liverpool
2. Alder Hey Children's Hospital

Hirschsprung's disease (HSCR) is a congenital disorder of the enteric nervous system (ENS) caused by a lack of enteric neurons and glia (aganglionosis) in the distal colon. The lack of ENS results in tonic contraction of the distal bowel leading to obstruction.

Proposed new therapies for HSCR as an alternative to the current surgical treatment include the use of neurospheres containing enteric neural crest precursor cells (ENSPCs). While it could be considered to graft these neurospheres into the aganglionic region to restore normal bowel function, it is currently unclear whether this approach will be sufficiently efficacious. We hypothesise that the success of ENSPC transplantation may depend on modulating the proliferation and/or migration of the grafted progenitor cells post-transplantation.

Signalling via the serotonin receptor 4 (5-HT4R) plays an important role in controlling proliferation and differentiation of enteric neurons but its involvement in the loss of functionality in the HSCR bowel is unknown. In this study, we aim to determine whether 5-HT4R signalling plays a role in HSCR bowel, by analysing both patient specimens and a murine model of HSCR.

Here, we will present preliminary data from immunostaining of HSCR patient samples for 5-HT4R expression, demonstrating its presence in aganglionic bowel. We are currently setting up a murine experimental model to further probe the role of serotonin in healthy and HSCR bowel.

To this effect, we have started to culture murine ENSPCs as neurospheres isolated from colon of CD1 mice. The characterisation of these neurospheres demonstrated that they contained ENSPCs, neurons, glia and 5-HT4 receptors. This will allow us to culture ganglionic and aganglionic neurospheres from the HSCR mouse model, and observe the effect of 5-HT4R agonism on neurospheres and ENSPCs in vitro and ex vivo using aganglionic bowel explants.

Keywords: Enteric nervous system, serotonin, hirschsprung's disease, cell therapy

Aberrant IP-10 (CXCL10) Signalling Impairs Neuronal Cellular Function: Impact on Skeletal Muscle Ageing

Caroline Staunton[1] , O. Ise[1], L. Abdul Kadir[1], E. Owen[1], R. Barrett-Jolley[1], M. Beadsworth[1], A. McArdle[1]

1. Institute of Ageing and Chronic Disease, University of Liverpool

Several physiological changes occur in skeletal muscle with age, including loss of motoneurons, morphological disruption of neuromuscular junctions, and upregulation of pro-inflammatory cytokines. These changes are associated with sarcopenia; the involuntary loss of skeletal muscle mass and strength. Muscle fibres from old mice show age-related changes in several degenerative pathways and a proposed aetiological factor of sarcopenia is chronic and systemic inflammation ("inflammaging") induced by cytokine accumulation.

Data have demonstrated that plasma levels of C-X-C motif chemokine 10 (CXCL10) also known as Interferon gamma-induced protein 10 (IP-10) are significantly elevated, even in very healthy older (>65 years old) individuals (Ford et al, under review and rodents (Owen et al, unpublished data). Additional novel data from our laboratory has demonstrated that skeletal muscle is a potential source of IP-10 (Owen et al, Gusnanti et al, unpublished data).

We hypothesised that the increased production of skeletal muscle-derived inflammatory mediators is a major contributor to sarcopenia and impaired neuromuscular function and specifically that the increased production of IP-10 by muscle results in local neuronal degeneration.

This study examined the neurotoxicological effects of an IP-10 challenge on motoneuron-like Neuroblastoma X Spinal Cord cells (NSC-34). Data showed that IP-10 significantly promoted hyperexcitability in neuronal cells, suggesting elevated IP-10 caused dysregulation of ion channels. Data demonstrated, for the first time, that IP-10 may act to disrupt neuronal ion channels at neuromuscular junctions at physiological concentrations evident in old age and provide a potential therapeutic target to preserve neuronal integrity and so protect against the development of sarcopenia.

Keywords: Skeletal Muscle, Ageing, Sarcopenia

Prefibrillar Aß Oligomers Cause Cognitive Impairment Accompanied by Abnormal Increase of in vivo Hippocampal Long-Term Potentiation (LTP) in Rats.

Yuhong Sun[1] , Bushra Almari[1], John Gigg[1], Michael K. Harte[1]

1. University of Manchester

Soluble Aß42 oligomers (Aßo) that aggregate from Aß42 peptides in early-stage of Alzheimer's disease (AD) are neurotoxic, causing synaptic dysfunction and neuronal death in brain regions vital for declarative memory, and resulting in AD pathologies and symptoms. This project aimed to investigate links between delayed effect of Aßo injection, synaptic dysfunction and cognitive deficits, by using the 7PA2 cell-line as a source of Aß.

Results: Firstly, dot-blot and Wes analyses established that prefibrillar Aß oligomers of ~48kDa and 6E10-reactive soluble Aß of ~153kDa were consistently present in the conditioned media (CM) from 7PA2 cells after 1 to 4 days of culturing. The amount of 6E10-reactive Aß increased over this period, while the level of prefibrillar oligomers was constant throughout. Secondly, female Lister Hooded rats received unilateral intrahippocampal injection of 10ul of 4-day concentrated 7PA2 CM. 7 days after treatment, they expressed significant deficits in novel object recognition memory compared to the vehicle controls. Another 7 days later, these rats also showed increased synaptic long-term potentiation in hippocampal area CA1 in vivo, evidenced by significantly larger slope and amplitudes of evoked fEPSP after high-frequency stimulation for 7PA2 animals under urethane anaesthesia.

Conlusion: Consequently, deficits in object memory induced by soluble Aß oligomers may be triggered by abnormal hippocampal information processing.

Keywords: Alzheimer's disease, prefibrillar Aß oligomer, 7PA2 cell-derived Aß, object recognition memory, in vivo long-term synaptic plasticity

EFFECTS OF HANDLING IN RATS AS A FORM OF ENVIRONMENTAL ENRICHMENT ON COGNITION IN THE SUB-CHRONIC PHENCYCLIDINE MODEL FOR SCHIZOPHRENIA

Linzi Watson[1], Matthew Burgess[1], Ben Grayson[1], Syeda Munni[1], Giovanni Podda[1], Nagi Idris[1], Joanna Neill[1]

1. University of Manchester

Introduction: Cognitive impairmentis a serious problem for many patients who suffer with schizophrenia. Environmental enrichment is recommended by NC3R's as a method of improving laboratory animal welfare; e.g. handling from early life. Neonatal handling was shown to prevent effects of sub-chronic phencyclidine (scPCP) to impair working memory performance (Tejedor-Real et al, 2007.Biological Psychiatry; Vol 61(7) (pp 865-872)). The aim of this study was to show that handling in adulthood could also prevent against scPCP induced deficits.

Methods: 4 groups of adult female Lister Hooded rats (n=10/group) were used; vehicle handled/non-handled and scPCP handled/non-handled. Rats in the handling groups were handled by 2 experimenters for 5 minutes/rat/day for 2 weeks. Rats then received either 2mg/kg PCP or 0.9% saline bi-daily for 7 days followed by 7 days wash-out and then tested in novel object recognition (NOR) (1-minute inter-trial interval-ITI) 2,4- and 7-weeks post-handling. Rats were also tested in NOR with a 6-hour ITI at 5 weeks post handling. Data were analysed by ANOVA and post-hoc students t-test.

Results: At 2 weeks post handling (1-minute ITI) scPCP handled rats successfully discriminated between the novel and familiar object ($p<0.001$) This effect persisted at 4 weeks ($p<0.01$) and 7 weeks ($p<0.05$). As expected, scPCP non-handled animals were unable to discriminate between the novel and familiar objects during these 3 NOR tasks. Following a 6-hour ITI, non-handled rats, both naïve and scPCP treated, were unable to discriminate between the novel and familiar object. However, handled rats in both groups showed a robust discrimination of the novel and familiar object; ($p<0.05$) and ($p<0.01$).

Conclusion: The results demonstrate that deficits in cognition normally induced by sub-chronic PCP administration can be prevented through handling of female Lister Hooded rats. Work to investigate the mechanism underlying could help us understand more of the pathology of schizophrenia.

Keywords: Schizophrenia, Cognition, Phencyclidine

Rescuing the paralysed phenotype of Munc18 mutant C. elegans

Khoula Afzal[1] , Jeff Barclay[1]

1. University of Liverpool

Mutations in Munc18, an essential protein for several stages of synaptic vesicle exocytosis, have been linked to early infantile epileptic encephalopathy. Null mutations in Munc18 and its homologs in worms (rop) and yeast (sec-1) are lethal, but not null mutations in the C. elegans homolog (unc-18). Consequently C. elegans prove a suitable model to investigate the effects of several loss-of-function mutations involving exocytosis, which in other species would be lethal. Through the process of ethylmethanesulfonate (EMS) mutagenesis, a novel strain, RESCUE, was identified in which the paralysed phenotype of unc-18 null mutants was rescued. Two novel mutations found in the rescue strain, present in the dgk-1 and sorf-2 genes were hypothesised to facilitate bypass of unc-18 function. Diacylglycerol kinase (dgk-1) catalyses the conversion of diacylglycerol (DAG) to phosphatidic acid (PA), thus functioning in synaptic transmission. Sorf-2 encodes the C. elegans homolog of WDR81, predicted to function in organelle fusion and endosomal transport. The aim of this project is to investigate the mechanisms through which the bypass of the unc-18 null mutation occurs. In this study we confirmed that RESCUE worms were significantly better at locomotion compared to unc-18 null mutants. Introduction of wild-type dgk-1 into RESCUE worms reversed the improvement in locomotion to unc-18 null levels suggesting necessity of the dgk-1 mutation for the rescued phenotype. Elevating DAG levels in unc-18 null mutants failed to improve locomotion, however, suggesting the dgk-1 mutation alone is not sufficient for phenotypic rescue. Further investigation into the sorf-2 mutation will lead to a better understanding of the mechanisms through which the two mutations bypass the unc-18 null mutation. This will further allow research into WDR81 function, little of which is known as of yet.

Keywords: C. elegans, Munc18, exocytosis, unc-18

Exploring prognostic biomarkers towards the surgical outcome for Temporal lobe epilepsy

Alvanah Ahmad[1] , Simon Keller[2], Laura Bonnett[3]

1. University of Liverpool

Introduction: Some people with epilepsy fail to achieve remission from seizures, despite medication. They may therefore be more suitable for surgery. The current study focuses on the separate lobules of the Cerebellum and the participants' clinical variables to observe the significant biomarkers in patients with mesial temporal lobe epilepsy. The Cerebellum is located in the hind part of the brain, consisting of 2 hemispheres. The Cerebellum communicates with neural networks which are responsible for a number of cognitive processes such as language, memory, posture, movement and emotions. The Cerebellum has been identified as a therapeutic target due to its extended networks to and from the hippocampus. The current study observed the anterior lobe of the Cerebellum (lobules I-V), the posterior lobe (lobules V-IX) and flocculondular lobe (lobule X). The main outcome is to observe whether these clinical variables contribute towards the outcome of surgery; whether patients are rendered seizure free or still experiencing seizures following surgery.

Method: 78 patients with mesial temporal lobe epilepsy and neuroradiologically evidenced unilateral Hippocampal sclerosis, underwent temporal lobe resection, they also had MRI scans to observe the cerebellum, the cortical thickness of its lobules and volume of grey matter. During the follow-up period, 27 patients experienced seizures after surgery; 51 patients were seizure free. Data from the CERES software was analysed using a binary logistic regression.

Results: The variable which was predictive of poor outcome was the side of surgery performed, however, there was no statistical significance. Increased cortical thickness and grey matter volume were predictors of good outcome, this is in agreement with previous literature, following surgical intervention. To date, this is the first study to observe mesial temporal lobe epilepsy in the Cerebellum. Future studies should include a larger sample size for statistical significance and generalisability. Furthermore, future studies must also focus on cortical thickness and side of surgery, to observe differences towards therapeutic outcomes.

Keywords: Epilepsy, Cerebellum

White matter tract microstructural alterations in Neuromyelitis Optica Spectrum Disorders with Aquaporin-4 and Myelin oligodendrocyte glycoprotein antibodies

Amal Alorainy[1] , Anu Jacob[2], Georg Meyer[1], Ofer Pasternak[3]

1. University of Liverpool
2. The Walton Centre , Liverpool
3. Harvard Medical School, Boston, USA

Introduction: Neuromyelitis Optica spectrum disorders (NMOSD) are rare relapsing inflammatory disorders of the central nervous system, mainly targeting the spinal cord and optic nerves. Though less well studied, it is increasingly recognised that the brain is also commonly affected. Antibodies to aquaporin-4 (AQP), and more recently, antibodies to myelin oligodendrocyte glycoprotein (MOG) have been identified in the sera of individuals with NMOSD.

Objectives: We aim to test the hypothesis that the inflammatory process in the brain is different between AQP- and MOG-positive NMOSD. We are using diffusion tensor imaging (DTI) to detect white matter tract alterations through direct patient-control comparisons.

Methodology: We scanned 39 patients with NMOSD (20 AQP, 19 MOG); all participants had a minimum of six-month remission. 32 age- and sex-matched healthy participants were scanned as controls. We obtained T1-weighted and DTI on a 3T MR Scanner for every participant. A free-water correction was applied before running tract-based-spatial statistics (TBSS)for the quantification of white matter diffusion metrics: fractional anisotropy (FA), mean (MD). Results were considered significant at p<0.05.

Results: A direct compersion of AQP and MOG showed no significant differences in FA and MD after correction for age .in compearing MOG with healthy controls there was no significant difference in FA or MD. When comparing AQP and healthy controls, there was no significant difference in MD, in FA, there was a significant decrease in the left corticospinal tract.

Conclusion: Our results indicate that there are differential neuroinflammatory processes in patients with AQP relative to MOG that may be quantified using diffusion MRI analysis.

Keywords: NMOSD , DTI, AQP-IgG ,MOG-IgG, TBSS

Drumming Induces Plasticity in Human Brains

Manal Alosaimi[1]

1. Institute of Population Health Sciences, University of Liverpool

Introduction: Brain plasticity is a life-long process that supports learning (Duffau, 2008). In humans, extensive and long-term training has been shown to induce volumetric structural and microstructural, measured with diffusion imaging, changes in grey and white matter. Musical training, for example, leads to increases in corpus collosum white matter volumes. The aim of this study was to quantify the time course of microstructural change, as measured with DTI, while participants learned a novel musical task.

Methods: Subjects: Fifteen healthy volunteers with no prior drumming experience took part after giving informed consent. Training: Participants were taught to play the drum-kit by a professional music teacher for approximately six months. Performance and progress were assessed by the teacher at each lesson and were formally evaluated after three months training.

Quantitative MRI Analysis: DTI data was pre-processed using a standard FSL workflow consisting of brain extraction (BET), eddy current correction, registration (FDT), and diffusion tensor model fitting (DTIFIT) to generate scalar DTI maps. Tract-Based Spatial Statistics (TBSS) scripts were used to co-register the DTI data into standard MNI space and to extract white matter tract skeletons.

To quantify change over time, a linear regression analysis was performed for each voxel in the co-registered images for each participant using the MATLAB polyfit function (Mathworks, V. 2018a).

Results: The TBSS analysis showed a significant change in the mean diffusion (MD, RD and L1) in skeletonised inferior-frontal white matter tracts (Fig 2, right). The skeleton projection step in TBSS is designed to reduce the effects of local mis-registration. For repeated measures (10-15 in our case) of the same participants, this misregistration is unlikely to be an issue, we therefore performed the regression analysis for each voxel in a voxel-based analysis (VBA, Schwartz et al., 2014). The VBA analysis shows significant change in left superior temporal sulcus for DTI parameters MD, RD and L1. Additionally, significant differences in the left anterior thalamic radiation DTI parameters MD, RD and L1 are seen (Fig 2, left).

Conclusions: Fitting linear regressors into a longitudinal DTI data and using the slope parameters as the basis for analysis enables us to characterise white matter tract changes in response to an intensive training task. Our results show statistically significant diffusivity changes in the inferior frontal and superior temporal white matter tracts.

Keywords: Brain plasticity

The Neural Correlates of Source Monitoring

Abdullah Alotaibi[1] , Georg Meyer[1], Richard Bentall[1], Jamaan Alghamdi[1, 1]

1. University of Liverpool

Research on hallucination (AVHs, or hearing voices) focused on patients with diagnosed psychiatric disorders. However , 5-10% of healthy population experience hallucination and meeting standard diagnostic criteria (Tien, 1991; van Os, Hanssen, Bijl, & Ravelli, 2000). The Launay-Slade Hallucination Scale (LSHS; Launay & Slade, 1981) has proven to be an effective method of identifying people within the healthy population who have high hallucination-proneness. The aim of this project is to test if there is a correlation between brain structure or functional activation and hallucination scores. Hallucination proneness in 69 healthy participants was assessed by using LSHS scale. T1 structure was done and used freesrufer to analyze this data. Freesurfer gave the volume and thickness of grey mater from the T1. The extracting data from freesurfer was correlated with LSHS scores and found positive significant correlation between left inferior, middle and transverse temporal thickness and scores. My result show that LSHS is proven effect mothed to correlate it to the participants data. These finding support the previous studies which used LSHS to correlate with their data.

Keywords: Hallucination

Structural and functional changes in brain language areas during the learning novel phonetic contrasts

Sahal Alotaibi[1] , Georg Meyer[1], Sophie Wuerger[1]

1. University of Liverpool

It is conventionally thought that speech production and perception are supported by two different brain areas: Broca's area in the left inferior frontal cortex for speech production, and Wernicke's area at the posterior end of the superior temporal cortex for speech reception. Recent data, however, has shown that the brain networks underlying speech reception and production are more complex than initially thought and - most importantly - closely integrated. These findings have led to the dual-steam model of speech processing. Primarily, the system bifurcates into two wide streams, a dorsal pathway maps sensory or phonological representations onto articulatory motor representations (how) and a ventral pathway, which is bilaterally organised, maps sensory or phonological representations onto lexical, conceptual and semantic representations (what).

In this study, baseline fMRI brain images are taken from English speaking healthy volunteers before the intervention. Then, they are taught novel phonetic contrasts from Arabic language to stimulate Broca's area. After completing the training sessions, the volunteers are got scanned again for comparison. Each MRI scan includes diffusion tensor imaging (DTI), functional MRI and structural MRI (MPRAGE). Structural and functional changes in the areas of interest (Wernicke's area and Broca's area) are being measured using MR image analysis.

Until the date of this abstract, data were collected from 14 subjects and the functional MRI results show two main findings. Firstly, the area of activation when they listen the novel phonics is different from the activation area when they listen to their own language. Secondly, the activation level in the area of the new language is changed after training.

During the next few months, the data collection will be continued from more participants, and more analysis methods will be applied such as structural and functional connectivity.

Keywords: fMRI, Broca's area, Wernicke's area

Structural and Functional Changes in the Brain Caused by Pitch Discrimination Training

Alanood Alsaleh[1]

1. University of Liverpool

Perceptual Learning has been shown to enhance performance on a pitch discrimination task and - we hypothesize - leads to structural and functional changes in the brain. Several investigations showed that auditory discrimination training has a good impact on language ability, reading skills and can reduce tinnitus severity .

This study will investigate the changes that associated with pitch discrimination training particularly functional and structural neural changes as well as interhemispheric interactions. This will be done by training a healthy adult population using adaptive and non-adaptive pitch discrimination methods while monitoring changes to brain function and structure using advanced MRI brain imaging before, during and after training sessions. Added to that a battery of quantitative image analysis methods will be used to investigate whether auditory discrimination learning has positive neural changes associated with an improvement in listening skills such as attention and discrimination.

Keywords: Pitch discrimination training

Caenorhabditis elegans as a model to study the functional role of small heat shock proteins in determining Charcot-Marie-Tooth type 2 disorder

Iman Aolymat[1], Lee Haynes[1], Jeff Barclay[1]

1. Institute of Translational Medicine, University of Liverpool

Background: Charcot-Marie-Tooth (CMT) syndrome is the most commonly inherited peripheral neuropathy characterised by progressive muscular and nervous system dysfunction. CMT has been categorised into demyelinating type 1 (CMT1) and axonal type 2 (CMT2) neuropathies. Unfortunately, the disorder is still incurable. Small heat shock proteins (sHSPs) are low molecular weight proteins mostly produced in response to stressful conditions. The most studied function of sHSPs is the prevention of protein misfolding and aggregation. Mutations in human HSPB1 and HSPB8 have been described in CMT2; however, the pathophysiological role of the associated mutated proteins remains unclear. We have created genetic models to investigate the pathophysiological impact of sHSP mutations in CMT2 using Caenorhabditis elegans (C. elegance).

Aim(s): Broadly, this project aims to create genetic models for CMT2 using C. elegans nematode which has been characterised as a strong model to study various genetic pathways associated with different diseases. These models can be used to verify pathophysiological impact of implicated mutated proteins. The models will be created by inserting the human HSPB1 and HSPB8 (wild-type (WT) and mutants) to investigate the role of these proteins and their mutations in CMT2. Additionally, the project aims to investigate the neuronal function of endogenous sHSPs in C. elegans. Finally, biochemical analysis and quantitative proteomics to characterize the effect of sHSPs mutations in vitro and in vivo are other project targets.

Results and conclusions: 1. The human HSPB1 WT and HSPB8 WT genes were cloned, mutagenized and expressed transgenically in C. elegans. **2.** The genetic models expressing human HSPB1 and HSPB8 (wild-type and mutants) were phenotypically screened in-depth throughout the lifespan of the animal. In terms of locomotion, strains overexpressing WT HSPBs showed normal locomotion while some strains overexpressing mutant HSPBs showed reduced locomotion pattern at different age groups. Regarding the chemosensory function, most of the models are chemotactically deficient including the WTs at different age groups. Synaptic function analysis showed a normal synaptic function for the WT worms and a suggested presynaptic defect in mutant HSPBs models. In vitro age-dependent neurodegeneration assays showed that the mutant HSPB1 Q175X overexpressing strains have axonal degeneration and loss of neuronal cell bodies at only young age groups. **3.** While working on CMT2 models creation, I investigated the broad function of sHSPs in neuronal dysfunction by phenotypic analyses of various genetic models over-/under-expressing endogenous sHSPs in C. elegans. The under-expression of certain endogenous sHSPs resulted in shorter lifespan, reduced locomotion and normal chemosensory function. Synaptic function analysis suggested a defect in neurotransmission in Hsf-1 and enhanced neurotransmitter (NT) release in Ok577 and Tm1221 over-aging. Hsp-16.1 over-expressing strains showed reduce lifespan and locomotion, normal chemosensation and enhanced NT release over-aging while Hsp-16.48 overexpressing strains have a lifespan similar to the N2, consistent pattern of movement over ageing and a normal chemosensory and synaptic functions. **4.** Some recombinant sHSPs (WTs & some mutants) are produced and purified and used for GST-pull down assays to identify interactions between HSPB1 WT OR HSPB1 Q175X and target proteins. The recombinant GST-HSPB1 Q175X showed defects in interaction with partner protein in comparison to the GST-HSPB1 WT. **5.** Proteomic analysis in CMT2 models using SILAN suggested a change in C. elegans proteome due to HPB1 Q175X mutation.

Future work (till the end of my PhD)

1. To identify HSPB1 partner proteins which the Q175X mutations negatively affected their binding through mass spectrometry.
2. To replicate the proteomic analysis in CMT2 models using SILAN.

Keywords: small heat shock proteins, Charcot-Marie-Tooth type 2

B09

Time-Frequency Analysis of the Neural Oscillations of Pain and Touch

Oda Asgard[1], Nicholas Fallon[1]

1. University of Liverpool

One of the most imperative aims of pain research is to find a neurological signature for pain. This includes creating models of the brain and nervous system able to track and predict the pain experience. Being able to track pain quantitively would provide valuable information regarding all brain areas involved with pain processing; further allowing insight to where pain becomes abnormal, as is the case with chronic pain conditions. However, current research is often skewed towards the ascending pathways and thus overlooking the affective response of the brain in pain perception. Therefore, we argue an investigation of the brain dynamics of pain with the integration of psychology of pain measures will provide a better understanding of the brain interconnectivity in response to pain. The current study takes use of mechanical pressure pain stimuli combined with time-frequency analysis of EEG data to investigate how the neural oscillations of alpha, beta and theta frequency bands differ between pain and touch conditions, where stimuli are delivered at various intensities. For time-frequency analysis we use event-related spectral perbutation (ERSP) to assess the changes in spectral power and frequency in response to the stimuli. In addition, behavioural measures concerning participants subjective pain ratings in the experiment are taken through a visual analogue scale (VAS) for pain after each stimulus during the experiment. Furthermore, participants psychological measures of Fear of Pain (FOP) and Pain Catastrophizing (PCS) is collected through questionnaires. We hypothesise that the intensity levels of pressure and pressure pain stimulation will differ significantly with regards to both subjective pain ratings and with the frequency band oscillations. Secondly, we hypothesise that the psychological measures FOP and PCS will moderate the relationship between subjectively reported pain and brain oscillatory activity in individuals.

Keywords: pain, pain perception, time-frequency analysis, event-related spectral perbutation (ERSP), mechanical pressure pain,

Luminance and chromatic contrast sensitivity for extended range of light levels

Maliha Ashraf[1], Sophie Wuerger[1]

1. University of Liverpool

Contrast sensitivity functions (CSF) are commonly used to characterise the sensitivity of the human visual system at different spatial scales, but little is known how the CSF changes from the mesopic range to a highly photopic range reflecting outdoor illumination levels.

The purpose of our study was to further characterise the CSF by measuring both achromatic and chromatic sensitivity for background luminance levels from 0.2 cd/m2 to 7000 cd/m2. Stimuli consisted of Gabor patches of different spatial frequencies and angular sizes, varying from 0.5 to 6 cpd and were displayed on an HDR display with luminance levels up to 15000 cd/m^2. Contrast sensitivity functions were measured in three directions in colour space, reflecting early post-receptoral processing stages: an achromatic (L+M) direction, a 'red-green' (L/(L-M)) direction, and a 'lime-violet' direction (S/(L+M). Within each session, observers were fully adapted to the fixed background luminance (0.2, 2, 20, 200, 2000 or 7000 cd/m2).

Our main finding is that the background luminance has a differential effect on achromatic contrast sensitivity compared to chromatic contrast sensitivity. The achromatic contrast sensitivity increases when going to higher background luminance levels up to 200 cd/m^2 and then shows a sharp decline when the background luminance is increased further. Compared to that the chromatic sensitivity curves do not show a significant sensitivity drop for higher luminance levels. Initial findings imply that our data is not consistent with a local cone contrast adaptation model. We've also observed variations in sensitivity magnitudes among observers especially in different age groups, and will be moving towards modelling age related contrast sensitivity function variations.

Keywords: Contrast Sensitivity, Human Color Vision, Psychophysics

The Effect of Gender on the Resting State Brain: An fMRI study of the Default Mode Network

Georgina Bailey[1] , Emma Smillie[1]

1. Liverpool Hope University

The default mode network (DMN) is a constellation of brain regions that are spatially distinct but functionally linked and show increased activation when at rest. Areas of the DMN have been implicated in multiple cognitive processes, which behavioural studies have highlighted as having gender differences.

This poster aims to investigate whether gender has an effect on DMN activity in two cohorts (n = 40; male = 20, female =20, split evenly across both groups) of healthy individuals (cohort A; Mean age = 23.90 cohort B; Mean age = 25) by analysing secondary resting state functional MRI data. Data was collected at Washington State University and all subjects were â€œtypicalâ€ reporting no significant psychological or neurological history.

For each participant T1-anatomical images and BOLD contrast functional images were collected. Functional connectivity was analysed using voxel-to-voxel and region of interest (ROI) seed-based correlation approaches.

It was hypothesised that females would show greater degree of resting-state functional connectivity across the DMN, as indicated by previous studies (Allen et al., 2011; Biswal et al., 2010; Bluhm et al., 2008). In particular that there would be evidence of gender differences within the posterior hub of the DMN.

Results showed no significant difference in functional connectivity between males and females overall. Independent sample t-tests using ROI analysis revealed significantly lower levels of connectivity for areas of the posterior hub and the left planum temporale and the left insular cortex. The hippocampus showed significant differences in functional connectivity with females having greater connectivity with the angular gyrus and posterior parietal cortex, while males showed a greater connectivity between the hippocampus and the opercular gyrus, precentral gyrus, lingual gyrus, insular gyrus, planum temporale and planum polare as well as with the sensorimotor and visual networks.

The results suggest that gender differences in the DMN may be mediated by regions implicated in the DMN subsystems.

Keywords: Functional connectivity, Default Mode Network (DMN), Gender, fMRI

Can We Emulate Pre-referential Knowledge in Adults and Infants? An EEG study

Lewis Ball[1] , Colin Bannard[1], Perrine Brusini[1], Eugenio Parise[2]

1. University of Liverpool
2. Lancaster University

Around the time of the vocabulary spurt, infants shift from an associationist mechanism of lexical acquisition to a referential mechanism of acquisition (Nazzi & Bertoncini, 2003). This transition appears to be sourced from the formation of referential connections between phonological and semantic representations in memory, beyond mere associations between the phonological and visual form (Friedrich, 2017). Yet does this mean that experienced speakers immediately attain referential knowledge when presented with new words, or does associative knowledge still serve as initial foundation for deeper levels of understanding?

Through a series of studies we will investigate this issue with the aid of the rich electrophysiological literature in the area of lexical acquisition. We are interested in measuring two different Event-Related Potentials (ERPs)- the N200-500 component and N400 component- which appear to reflect associative and referential word processing respectively (Friedrich & Friederici, 2004; 2011; Kutas & Federmeier, 2010).

Beginning with adults we will present novel words and objects to participants. In a subsequent test phase we will measure participants' ERPs in response to these words, and compare to ERPs produced by familiar words. Although we expect to observe sound referential knowledge for familiar words (i.e. a detectable N400), equivalent levels of understanding for novel words is debatable. With just brief exposure to novel words and their referents, we expect the strength of representations assembled during learning to be sufficient enough to provide associative knowledge (reflected via an N200-500), yet are equally too weak to elicit referential understanding (absent N400).

These results will be compared to results from an infant (12-18 months) sample using a similar paradigm. Such methods will not only allow us to examine age differences in understanding familiar words, but also explore similarities in very early representations for new words, which may not be so different across experienced and novice speakers.

Keywords: Word knowledge, Development, EEG, N400, Semantics

Investigation of a Novel Short Isoform of Monoamine Oxidase A (MAOA)

Sophie Breen[1] , Alec Simpson[1], Jill Bubb[1]

1. University of Liverpool

Monoamine oxidase A (MAOA) is a mitochondrial outer membrane (MOM) bound flavoenzyme which catalyses the oxidative deamination of biogenic amine neurotransmitters and has been implicated in the pathophysiology of many neuropsychiatric disorders. Differential splicing of MAOA gene produces two mRNA transcripts encoding two distinct protein isoforms; here we investigate the short isoform (sMAOA). We hypothesised that the amino terminus truncation of sMAOA relative to the canonical isoform (lMAOA) would alter protein targeting, preventing its localisation to the mitochondria. Building on work previously undertaken by our institution, we report the transient transfection of HaCaT cells with a plasmid comprising a hemagglutinin tagged sMAOA gene insert. A western blot enabled us to determine if lMAOA and sMAOA were dimerising in the MOM. It was also used to select appropriate primary antibodies for immunocytochemistry, permitting us to visualise sMAOA's cellular location. The results provide evidence that lMAOA is monomeric in the MOM. Additionally, it was shown that sMAOA's targeting is not altered by its relative amino terminus truncation. Further experimentation to determine the function of sMAOA is critical to further our understanding of the cause of neuropsychiatric disorders.

Keywords: Monoamine oxidase A, MAOA, neuropsychiatric disorders, sMAOA isoform, biogenic amines, dopamine, noradrenaline, adrenaline, serotonin, histamine

THE ROLE OF NOTCH SIGNALLING IN AGANGLIONIC HIRSCHSPRUNG BOWEL: A STEP TOWARDS AUTOLOGOUS THERAPIES FOR CHILDREN WITH HIRSCHSPRUNG'S DISEASE

Sumita Chhabra[1, 2], Jenna Doherty[1], Sarah Almond[2], Simon Kenny[1, 2], Patricia Murray[1], David Edgar[1], Bettina Wilm[1]

1. University of Liverpool
2. Alder Hey Children's Hospital

Approximately 270 babies are born with Hirschsprung's disease each year in the UK; a condition which is characterised by a deficiency of the enteric nervous system in the distal bowel to a variable extent. Despite surgical removal of the affected bowel, long-term outcomes for patients remain poor.

Canonical Notch signalling has been demonstrated to regulate proliferation and neuronal differentiation of human enteric nervous system progenitor cells (ENSPCs) cultured as neurospheres in vitro. Unexpectedly, we have recently shown that ENSPCs can also be isolated from thickened nerve trunks characteristic of aganglionic gut of Hirschsprung patients. Here we aim to determine if Notch signalling is also present in aganglionic bowel and cultured ENSPCs to assess whether modulation of Notch signalling may offer a novel therapy for treatment of Hirschsprung's disease.

Methods: Expression of key Notch receptors was determined using immunofluorescence in aganglionic and ganglionic Hirschsprung's gut samples obtained from patients during pull-through surgery. Primary ganglionic and aganglionic neurospheres were formed following culture of ENSPCs derived from the myenteric plexus.

Results: Notch receptors 2, 3 and 4 were generally distributed within thickened nerve trunks in aganglionic colon, similarly to distribution in normal enteric nervous system ganglia. Expression of these Notch receptors was retained by the cells in cultured primary aganglionic neurospheres and co-localisation with ENSPC was visualised with confocal microscopy. In addition, progenitor cells derived from dissociated primary neurospheres also expressed Notch receptors 2, 3 and 4.

Conclusion: Since Notch receptors were expressed in aganglionic gut we hypothesize that Notch signalling can regulate the maintenance and differentiation of ENSPCs from aganglionic Hirschsprung bowel in vivo and thereby offer a potential tool to help develop novel therapies for children with Hirschsprung's disease. Our current work will now further assess the functional effects of Notch signalling in ENSPCs within aganglionic and ganglionic bowel-derived neurospheres.

Keywords: Hirschsprung's Disease, Enteric nervous system, Notch Signalling, enteric neurons

Does social touch deprivation in early development influence CT-sensitivity in adulthood? A quantitative comparison between foster care-leavers and non-care leavers.

Shaunna Devine[1] , Francis McGlone[1], Elizabeth Stockton[1] , Adarsh Makdani[1], Paula Trotter[1]

1. Liverpool John Moores University

Background: C-Tactile afferents (CTs) are slowly conducting nerve fibres present in human hairy skin, which have been identified to optimally respond to the medium-velocity stroking sensations experienced during a human caress. One proposed role for these nerve fibres is encoding the rewarding properties of social touch. Like any neuronal system, a lack of CT-stimulation during the early developmental period may lead to atypical CT-system development, effects of which may prevail into adulthood.

Aims: to investigate the effects of social touch deprivation in early development on CT-sensitivity in adulthood. It was hypothesised that care-leavers (those spending at least one year in foster care) would report experiencing significantly lower levels of social touch in childhood than non-care leavers. In turn, it was hypothesised that sensitivity to CT-optimal compared to non-optimal touch would be reduced in care-leavers.

Methods: a sample of 14 care-leavers and 32 non-care leavers (mean ± SD age = 21.26 ± 1.82, 40 females, 6 males) were recruited through opportunity sampling. CT-optimal and non-optimal stroking touch was applied to the left ventral forearm and participants rated perceived pleasantness using a visual analogue scale. Stroking touch was delivered robotically, as well as socially via the experimenter's cotton-gloved hand.

Results: care-leavers reported significantly lower levels of positive touch in childhood compared to non-care leavers. No significant differences between robotic and social touch were identified. A significant care-leaver status x velocity interaction was identified. The typically observed inverted U-shaped relationship between stroking velocity and pleasantness was observed for non-care leavers, but not for care-leavers, supporting the hypothesis.

Conclusions: the results of this study supports the hypothesis that a lack of CT-activation through social touch interactions in the early developmental period may lead to atypical development of the CT-system, effects of which may prevail into adulthood. Further investigation to confirm this mechanism is required.

Keywords: C-Tactile afferents, social touch, foster care-leavers, touch deprivation, early development

Characterising the Long Interspersed Element-1 (LINE1) methylation landscape in healthy cognitive ageing

Ana Illera-Lopez[1], Abigail Savage[1], Vivien J Bubb[1], John P Quinn[1]

1. Institute of Translational Medicine, University of Liverpool

A subset of non-coding repetitive elements named Long-Interspersed Nuclear Elements (LINE1s) has been shown to have a role in adult neurogenesis and may contribute positively towards memory. Such elements have the ability to transpose in the genome. It has been found that the majority of LINE1 repetitive elements are the offspring of a set of specific LINE1s termed 'hot' LINE1s which are actively transcribed. DNA methylation is an epigenetic mechanism whereby the activity of these elements could be regulated in the genome. With this in mind, the aims of this research were as follows: 1) to assess the methylation status of LINE1 elements globally, and of four major 'hot' LINE1s specifically in order to evaluate their potential to be transcribed; and, 2) to determine presence/absence polymorphisms of these 'hot' LINE1 elements in the aged population, which could result in different levels of LINE1 activity.

Genomic DNA was isolated from temporal cortex and blood of healthy aged people and Alzheimer's disease (AD) patients. To analyse the methylation state of LINE1 elements the following methods were employed: i) bisulphite treatment and pyrosequencing ii) CpG methylation pulldown to separate methylated from unmethylated DNA fraction iii) PCR genotyping to explore hot LINE1 methylation status in the population. To detect presence/absence polymorphisms in the population PCR genotyping was undertaken.

Our analysis suggests that there is a significantly higher level of methylation in the blood compared to the temporal cortex, which is suggestive of differential tissue-specific regulation of LINE1 elements. Furthermore, the allele harbouring the active LINE1 insertions shows significantly higher level of methylation compared to the allele lacking the active L1 insertion, which is suggestive of a silencing role of LINE1s. There are no significant differences when looking at presence/absence polymorphisms between individuals. This suggest that polymorphism in presence or absence is less relevant than methylation for levels of LINE1 in the brain.

Keywords: LINE1, DNA methylation, PCR, healthy cognitive ageing

Volumetric analysis of the insular cortex in patients with temporal lobe epilepsy

Mohamed Isse[1] , Bernd Weber[2], Simon Keller[1]

1. University of Liverpool
2. University of Bonn

Background: Epilepsy is a common neurological disorder affecting over 50 million people worldwide. Patients with refractory temporal lobe epilepsy (TLE) may be treated with temporal lobe surgical resection, which offers seizure freedom to at least 50% of patients. There are multiple theories which attempt to account for the seizure failure rate, including 'temporal plus epilepsies', which hypothesises the existence of an extra-temporal seizure focus, though this has not been definitively confirmed.

Objectives: Determine whether there is insular atrophy in patients with TLE. Further outcomes include looking at the relationship between insular volume and the presence of febrile seizures, secondary generalised tonic-clonic seizures (SGTCS), and its relationship with surgical outcome.

Methods: Magnetic resonance imaging (MRI) of 77 patients and 36 healthy controls were quantitatively analysed using manual stereological techniques. Left and right insular volumes were obtained, and multivariate analysis controlling for sex and age was carried out using SPSS with post hoc Bonferroni correction.

Results: There was a significant difference in both left ($F=20.27$, $p<0.001$) and right ($F=19.16$, $P<0.001$) insular volumes between patients with TLE compared with controls. Insular volumes were reduced bilaterally in both left TLE (L-insula $p<0.0001$, R- $p<0.0001$) and right sided TLE (L- $p=0.0003$, R- $p=0.006$) compared to controls. There was no significant difference in insular volume between patients with and without a history of febrile seizures, and in those with and without the presence of SGTCS. Further analysis found no relationship between insular volume and post-surgical outcome at an average of two years after surgery.

Conclusion: Our findings implicate the insula in temporal lobe epilepsy. Already existing dense neuronal connections between the insula and the rest of the brain may help to explain the potential underlying pathophysiological process. This study assessed gross insular volume and hence did not differentiate between functionally distinct areas within the insula itself. Further image analysis techniques such as DTI are needed to expound on these promising results.

Keywords: Neuroscience, Neuro-imaging, Temporal Lobe Epilepsy, Insula

Microneurography: My bounty is as boundless as the C

Adarsh Makdani[1] , Andrew Marshall[2], Francis O'Neill[3], Francis McGlone[1, 4]

1. Liverpool John Moores University
2. Pain Research Institute, University of Liverpool
3. Dept. of Oral Surgery, Liverpool University Dental Hospital
4. Institute of Psychology, Health & Society, University of Liverpool

Microneurography is a neurophysiological technique developed (relatively recently) by Åke Vallbo and KarlErik Hagbarth in the 1960s, which allows the real-time monitoring and recording of peripheral nerve impulses in awake human subjects. One of the first studies[2] investigated the discharge characteristics of mechanosensitive afferents in the skin—and included recordings of mass activity from bundles of mechanoreceptors, and single-fibre recordings— activity from single mechanosensitive myelinated afferent nerve fibres. The technique was adapted to allow recordings from single C-Fibres[3]- initially dismissed as “not possible”![4]

Intraneural Microstimulation (INMS) during Microneurography uniquely enables investigations into the sensations and conscious percept associated with direct electrical stimulation of single nerve fibres, revealing even more about their function and specificity.

Microneurography underpins our understanding of human neurophysiology –from mapping and characterising cutaneous receptor complexes, to identifying mechanisms, pathways, and cortical representations. By recording from and stimulating peripheral nerves (A-fibres and C-fibres), we understand more about that which drives the human somatsensory experience, including discriminative touch, temperature sensation, pain, itch, and pleasant, affiliative touch.

The Somatoensory and Affective Neuroscience group (SomAffect), LJMU has one of the few labs in the world which focuses on single-fibre, a.k.a. single-unit Microneurography; aiming to discover more through exploring a variety of body sites (and nerve bundles), applying novel stimuli and ligands to the receptive fields of single units, and testing the responses (both psychological and physiological) under different conditions.

A selection of recordings will be presented to showcase the power of the technique, and specifically to highlight the boundless variety and importance of C-fibres - the nerve fibres that drive emotionally charged sensations such as Pain, Itch and Affective Touch.

References:

1. Title from - Shakespeare, W. The Tragedy of Romeo and Juliet (A2.S2:L133, P60). Mr. William Shakespeare's Comedies, Histories, & Tragedies. 1:53-79. (1623)
2. Vallbo, A. & Hagbarth, KE. Activity from skin mechanoreceptors recorded percutaneously in awake human subjects. Exp Neurol, 21(3):270-89. (1968)
3. Torebjörk, HE. & Hallin, RG. Responses in human A and C fibres to repeated electrical intradermal stimulation. Journal of Neurology, Neurosurgery & Psychiatry 37:653-664. (1974)
4. Namer, B. Microneurography and Intraneural Microstimulation. Encyclopedia of Pain. 1846-1850. (2013)

Research supported by: Pain Relief Foundation, Liverpool

Keywords: Electrophysiology, C Fibres, Peripheral Nervous System, Somatosensation, Pain, Itch, Affective Touch

Genetic variation of a human specific SVA element in the NEK1 locus and its association with ALS risk.

Jack Marshall[1] , Richard Mead[2], Pamela Shaw[2], Vivien Bubb[1], John Quinn[1]

1. University of Liverpool
2. University of Sheffield

The genetic basis for both sporadic and familial forms of Amyotrophic Lateral Sclerosis (ALS) is now partially known, with nearly 30 genes known to be associated with the disease. Concurrently there is a growing awareness of non-coding variants as risk factors for many diseases including ALS. Major components of such uncharacterised genetic risk which is predominantly non-coding are the non-long terminal repeat retrotransposons (non-LTR RTE); constituting approximately 34% of the human genome. Loss of function variants of the kinase NEK1 have been found to be associated with ALS risk in a small number of patients; we now address non-coding variation at this locus and characterise the potential for such variation to impact on NEK1 gene regulation. We have determined genetic variation of an intronic SINE-VNTR-Alu (SVA) retrotransposon element which was present in all individuals analysed and was found to be polymorphic in three domains: the CCCTCT hexameric repeat (CT element), variable number tandem repeat (VNTR) and Poly A tail. Interestingly, we defined four alleles of the CT element in the population examined, two of which were only present in the ALS cohort. Furthermore, we demonstrated that this SVA was functional in a reporter gene assay leading to significant repression in comparison to the minimal promoter alone. We hypothesise that variants, albeit rare, within the CT element of this SVA could be associated with increased ALS risk and that the SVA could serve as a potential transcriptional regulatory domain at the NEK1 locus, acting in a tissue specific and stimulus inducible manner.

Keywords: SVA, NEK1, ALS, Retrotransposons, Genetics

Multispectral Optoacoustic Tomography for the Characterisation of Tumour Perfusion

Anika Masud[1] , Harish Poptani[1], Jack Sharkey[1]

1. Institute of Translational Medicine, University of Liverpool

Tumour growth depends on the presence of a well vascularised network that can supply nutrients and oxygen to tumor cells. Rapid proliferating tumour cells however develop faster than their surrounding local blood supply and as such are forced to adapt by creating their own avascular microenvironment devoid of oxygen i.e. hypoxic. For this reason, hypoxia, among other factors, plays a fundamental role in tumorigenesis which is why it has been implicated in diminished treatment responses. Although there have been substantial advances in the treatment of different cancers, there remains a number of tumour types that do not optimally respond to any of the available treatments yet. Non-invasive pre-clinical imaging yield potential insight to facilitate with the understanding of the mechanisms underlying tumour progression by allowing real-time, high sensitivity visualisation of a subject. These in vivo techniques can be translated to allow diagnosis for the early detection of cancers in human patients. In this study, we performed in vivo Multispectral Optoacoustic Tomography, Bioluminescence and Doppler Ultrasound imaging to assess vascularisation and growth as a potential marker for reduced oxygenation in tumour bearing mice over a set amount of days. Immunohistochemical methods based on EF5 antibody detection of hypoxia marker and H&E staining were also performed on dissected tumour samples. Our data from each modality suggest that perfusion significantly drops with tumor growth which is indicative of poor vascularization and hypoxia. This was confirmed by immunohistochemical testing where stronger fluorescence from inner tumour mass samples were observed in contrast with outer tumour sections suggesting a prominent oxygen deficient core.

Keywords: Tomography, MSOT, Tumour, Hypoxia

Molecular Identification of the Clozapine Transporter

Wedad Mawkili[1] , David Dickens[1]

1. University of Liverpool

Schizophrenia is a severe mental disorder that affects more than 21 million people worldwide. Schizophrenia is a treatable condition and currently, treatment mostly involves the administration of antipsychotic drugs combined with psychological therapies. Over 22 FDA-approved antipsychotics are used to treat schizophrenia, clozapine is the most effective drug in treatment of refractory schizophrenia and despite that, its use is restricted due to its fatal haematological adverse reaction, agranulocytosis, which occurs in approximately 1% of treated patients. Clozapine movement across membranes is characterised by saturation and also it can be inhibited by other chemicals such as verapamil, which is compatible with a carrier-mediated process. Therefore, the molecular identification of the clozapine transporter will be helpful in understanding clozapine's efficacy at BBB and safety profile at neutrophil.

In order to identify the clozapine transporter a genome-wide loss of function genetics screen using a knockout approach (retrovirus gene trap) will be performed. Gene-trap retrovirus is produced in HEK293T cells using gene-trap vectors consisting of a promotor less reporter gene (GFP) flanked by splice acceptor (SA) and polyadenylation sequence (polyA). In retroviral gene trapping, a DNA sequence is inserted randomly throughout the intron of a gene. Therefore, it prevents proper exon-exon splicing, and introduces a polyadenylation signal so that transcription of the relative gene is terminated resulting in knockout of this gene. Then, as a selection pressure, the mutagenized HAP1 cells will be treated with a cytotoxic dose of clozapine (100 Î¼M), this concentration of clozapine was determined via cell viability assays (ATP content) and colony formation assays (crystal violet). Only cells that lack the clozapine transporter will survive as the drug will not be taken up into the cells. Genome-wide insertional mutagenesis approach in near haploid cell line allow assessing gene-trap loss of function mutations that would rescue cells from clozapine induced cytotoxicity.

Keywords: Clozapine, Carrier-mediated transport, Genome screen

An Evaluation of an SVA Retrotransposon within LRRK2 as a Potential Risk Factor for Parkinson's Disease

Lauren Owens[1] , Ben Middlehurst[1], John Quinn[1], Jill Bubb[1]

1. Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool

Mutations in the LRRK2 locus are considered a major genetic contributor to Parkinson's disease (PD). The most studied genetic variation is within coding regions, leading to potential alterations in protein structure and function. However, the majority of variation in the genome is found within non-coding regions. This variation, often found in potential regulatory DNA, may change gene expression or alternate splicing which may subsequently alter protein levels and function. A major source of non-coding variation are retrotransposons: a class of DNA elements which can 'copy-and-paste' themselves into new genomic locations. These include the SVA class, of which an insertion is present in intron 44 of LRRK2. We aimed to (1) evaluate whether polymorphism in this SVA could pose a risk-factor for PD, and (2) evaluate the functional effect of the SVA on gene expression.

DNA samples from PD cases and matched controls were genotyped. Polymorphism was observed in two components of the SVA but there was no significant difference in allele or genotype frequencies between cases and controls in this preliminary study (n=355).

The effect on gene expression was assessed using a luciferase reporter gene cassette, measuring luminescence to assess the regulatory properties of the SVA in HEK293 cells. Compared to cells transfected with a control vector, the SVA significantly decreased expression ($p<0.001$). This effect was independent of orientation.

To conclude, polymorphism in the SVA within LRRK2 showed no association with PD in this small cohort. However, the SVA is able to regulate gene expression. Polymorphism within the SVA could therefore be important for differential gene expression and in response to stimuli or stress. As a regulatory domain the SVA is likely to be regulated in a tissue-specific and stimulus-inducible manner and therefore a potential mediator of Gene x Environment interactions in PD.

Keywords: Parkinson's disease, genetics

Rapid white-matter microstructural changes induced by learning: A Diffusion Tensor Imaging Study

Michal Paradysz[1], G. Meyer[1], N. T. Uomini[1], L. S. Barham[1]

1. University of Liverpool

Synaptic plasticity, resulting in functional brain changes during learning is a well established mechanism supporting learning. Recent work has shown micro-structural changes in white matter within 24 hours of learning a new skill. Very little is known about this mechanism.

The aim of this study is to identify white matter micro-structural changes. The training task chosen was flint knapping, making stone age tools. Fourteen participants underwent a 2 hour training.

To acquire diffusion tensor imaging data each participant attended two fMRI scanning sessions, one before training and one the day after.

Results show significant, mainly unilateral decreases in mean, axial and radial diffusivity in white matter structures of the right hemisphere, predominantly in the body of the corpus callosum (bCC) and the anterior & posterior limbs of the internal capsule (aIC & pIC). These regions have been found to interconnect multiple cortical structures which have been evidenced to be involved in skilled and precise movements. No significant changes in fractional anisotropy were observed.

The micro-structural changes which occur in these areas have not yet been observed in studies utilising such short motor training period and may have been induced by the modulation of fiber organisation and myelination patterns.

The results may pave the way towards more effective rehabilitation designs for patients with neurological injury or disease.

Keywords: Rapid synaptic plasticity, Motor skill Learning, Diffusion Tensor Imaging

The Antidepressant AV-101 is a Substrate for LAT1 (SLC7A5) at the Blood-Brain Barrier

Waseema Patel[1] , Mark A. Smith[2], H. Ralph Snodgrass[2], Munir Pirmohamed[1], Ana Alfirevic[1], David Dickens[1]

1. University of Liverpool
2. VistaGen Therapeutics Inc

Major depressive disorder is the leading cause of disability worldwide; the prodrug of 7-chlorokynurenic acid, AV-101 is currently in phase II clinical trials as an adjunct antidepressant therapy. The movement of compounds across the blood-brain barrier (BBB) represents a bottleneck in the delivery of neurotherapeutics however, the amino acid transporter LAT1 (SLC7A5), allows the passage of neurotherapeutics across the BBB. We investigated whether AV-101 is a substrate of LAT1 and characterised the movement of AV-101 through LAT1. Using [14C]-AV-101, we followed the uptake of the compound in HEK 293 cells stably overexpressing LAT1 or matched control cells, with the inhibitor JPH203 used to test for specificity. We found AV-101 (10µM) uptake to be 689.7±69.5 pmoles/million cells in LAT1 expressing cells compared to 76.5 ± 9.8 pmoles/million cells (n=3, $p<0.05$) in control cells. Addition of the LAT1 inhibitor, JPH203, (10µM) reduced this uptake to 21.8±2.4 pmoles/million cells (n=3, $p<0.05$) and 14.3±1.4 pmoles/million cells (n=3, $p<0.05$) in LAT1 expressing and control cells, respectively, indicating AV-101 was indeed being transported via LAT1. We also characterised the uptake kinetics of AV-101; the Vmax was 4522±1016 pmoles/million cells/min and the Km was 1799±372.5 µM. In comparison, the model LAT1 substrate, phenylalanine (10µM), showed an uptake of 754.2 ± 103.8 pmoles/million cells in LAT1 expressing cells compared to 319.8±34.25 pmoles/million cells (n=3, $p<0.05$) in control cells. Overall, AV-101 showed a LAT1-mediated uptake of 613.1±77.8 pmoles/million cells whilst phenylalanine had an uptake of 434.4±121.1 pmoles/million cells. Together with the uptake data, these similarities in LAT1-mediated uptake suggested that AV-101 showed a greater selectivity for LAT1 in comparison to phenylalanine. Future experiments will determine whether AV-101 is a substrate of other transporters. Additionally, we will perform a genotype to phenotype approach to assess if genetic variants in LAT1 and additional candidate genes correlate with AV-101 efficacy.

Keywords: LAT1, BBB, AV-101, Depression

Investigating the contribution of human-specific DNA on pain pathways and associations with pain phenotypes.

Emma Price[1] , Neil Pendleton[2], Anthony Payton[3], Daniel Carr[4], Daniel Kemp[1], Bernhard Frank[5], Vivien Bubb[1], John Quinn[1]

1. Neurobiology Research Group, Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool
2. Division of Neuroscience and Experimental Psychology, Faculty of Biology, Medicine and Health, School of Medical Sciences, The University of Manchester
3. Division of Informatics, Imaging and Data Sciences, School of Health Sciences, The University of Manchester
4. Wolfson Centre for Personalised Medicine, Medical Research Council (MRC) Centre for Drug Safety Science, Department of Molecular and Clinical Pharmacology, University of Liverpool
5. Department of Pain Medicine, The Walton Centre NHS Foundation Trust

Pain has evolved as a critical response to noxious stimuli, to ensure survival. Repetitive DNA sequences, known as SVA retrotransposons (SVAs), have emerged throughout primate evolution and have helped shape the human genome. SVAs function as regulatory DNA elements affecting gene expression in a species-specific and tissue-specific manner. SVAs are polymorphic, contributing to genetic variation in human populations, yet certain polymorphisms have also been associated with disease. Using bioinformatic analysis, we identified an enrichment of SVAs on chromosome 17 at the locus encoding ion channels which detect noxious stimuli; TRPV1 & TRPV3. Analysis of gene expression data and current reports in the literature indicate the expression patterns of TRPV3 differ between mice and humans. We hypothesise that the SVA insertion at TRPV1 & TRPV3 in human genome has contributed to human specific expression of TRPV3. The first aim of this research was to assess the regulatory potential of the SVA insertion on TRPV1 & TRPV3 expression in human cell lines using a genetic modification technique known as CRISPR. The second aim was to explore the genetic polymorphism of the SVA and investigate if there was any association with pain phenotype. We have developed a robust CRISPR protocol which enables the study of regulatory DNA sequences on target gene expression and preliminary data supports the SVAs regulatory role on TRPV3 expression. We also identified at least four SVA polymorphisms in the general population and found associations between a distinct genotype and pain related phenotypes. These results may explain the human specific expression of TRPV3 and explain the lack of clinical interventions targeting TRPV3 from research using rodent models. Associations with SVA polymorphism and pain phenotype are now being further validated in larger pain cohorts which may potentially be used as a biomarker for risk or response to therapeutics.

Keywords: Chronic pain, genetics, animal models, evolution.

Assessment of DRG surface binding by CRPS-serum-IgG using primary mouse cells

Serena Sensi[1] , Dean Naisbitt[1], Philip Rudland[1], Angela Platt-Higgins[1], Andreas Goebel[1]

1. University of Liverpool

Recent works suggest that in some patients with CRPS there is an autoantibody response against surface markers on primary neurons, but cellular and molecular targets are unknown. Using IHC staining we investigate surface epitope binding of CRPS-serum-IgG to murine primary dorsal root ganglion cells.

Mice were injected daily intra-peritoneally (for up to 13 days) with either affinity-purified plasma-IgG from patients with persistent CRPS, or with IgG derived from healthy controls, then a small skin-muscle incision was applied to the right hind paw under general anaesthesia. Finally mice were perfused with 4% Paraformaldehyde and Dorsal Root Ganglia (DRGs) corresponding to the incised paw were harvested, fixed in 4% Paraformaldehyde and paraffin embedded for IHC staining. Paraffin slides were firstly stained with goat anti-human-IgG-HRP to detect CRPS/HC IgGs in tissue and in case of no staining slides were then stained with affinity purified CRPS/HC-IgGs and then with anti-human-IgG-HRP

Only in rare cases it was possible to detect CRPS-IgG in slides stained directly with anti-human-IgG-HRP, some neurons were stained and these had high IgG concentration only in the cytoplasm. When slides were stained with affinity purified CRPS/HC IgG and then with an anti-human-IgG-HRP, some neurons were stained and these had high IgG only in the cytoplasm, in particular same neurons were stained with different CRPS patient IgG.

In conclusion, in this assessment of DRG surface binding by CRPS serum IgG, some neurons have a strong and standardised binding with human IgGs in the cytoplasm.

Support: Pain Relief Foundation, Liverpool.

Keywords: Chronic Pain

The impact of age-related hearing loss on speech perception networks in the brain

Kate Slade[1], Helen Nuttall[1], Chris Plack[1]

1. Lancaster University

Hearing loss has a huge impact on our aging population, affecting nearly 42% of individuals over 50 years and 71% of those aged over 70. Coping with hearing loss can dramatically affect the quality of life for older adults; leading to social isolation, decreased wellbeing and increased chance of cognitive decline. Research suggests that individuals with hearing loss make greater use of cortical top-down resources during speech perception, to compensate for the impaired peripheral auditory system. However, it is currently unclear how the higher-level cortical pathways are affected by age-related hearing loss, and by adverse listening situations (for example, perceiving speech in background noise). This study sets out to understand the relationship between speech perception, activity in the auditory cortex, and activity in the premotor cortex, to investigate if speech perception is complemented by top-down motor networks following age-related hearing loss. Knowing this will help to direct appropriate intervention strategies for older adults with hearing loss.

Older adults (60-85 years) both with and without hearing loss, as well as adults (18-30 years) without hearing loss will be recruited. Participants will undergo disruptive transcranial magnetic stimulation to the premotor cortex, to supress the influence of top-down premotor pathways. Cortical auditory event-related potentials and behavioural speech perception abilities will be measured before and after stimulation. It is hypothesised that if auditory cortex activity is compensated by top-down premotor cortex resources, then the disruptive effect of stimulation will have the greatest effect on cortical auditory event-related potentials, and speech perception scores in the hearing loss group, independently of age. This research will ultimately inform whether interventions should be directed towards supporting auditory or compensatory motor resources.

Keywords: Speech Perception, Auditory Cortex, TMS, EEG, ERP, Premotor Cortex, Hearing Loss

The investigative analysis of the common and rare genotype and allele frequencies of a REST VNTR found in control and ALS samples

Farah Tahmasebi[1]

1. University of Liverpool

Amyotrophic lateral Sclerosis (ALS) is a fatal neurodegenerative disease with poorly understood underlying pathogenic mechanisms and as a result there is an absence of effective therapies or preventative treatments for the disease. Previous studies have stated that the multi-staged aetiology of ALS is caused by a combination of genetic, epigenetic and environmental factors with GWAS studies identifying further some of the genetic risk polymorphisms with ALS progression. A gene implicated in several neurodegenerative diseases is RE-1 Silencing Transcription Factor (REST) also known as Neuron Restrictive Silencer Factor (NRSF) with studies linking the gene induction and accumulation to neuroprotection and dysregulation linking to neurodegenerative disease. Previous studies have identified a Variable Number Tandem Repeat (VNTR) upstream of the promotor region of the REST gene that is polymorphic and could potentially drive different levels of REST/NRSF expression making it all the more interesting and potentially implicating it in the transcriptional differences of REST/NRSF witnessed in different neurodegenerative diseases. Previous work has shown this VNTR to have several polymorphisms, with the three most common having 7, 9 and 12 repeats. The purpose of this research was to investigate rare variants and their disease specificity in ALS with data analysis of ExpansionHunter Software data which identified a rare 6 repeat variation only in the ALS cohort and not in the control cohort.

Keywords: Functional Genetics Neurobiology ALS

Age differences in prefrontal oxygenation during temporal associations in memory: an fNIRS study

Deborah Talamonti[1] , Catharine Montgomery[1], Dan P.A. Clark[2], Davide Bruno[1]

1. Liverpool John Moores University
2. Liverpool Hope University

Older adults perform worse in free recall memory tasks relative to younger adults (Kahana et al., 2002). Ageing has been related to decline of brain activation and brain frontal lateralization (HAROLD) during cognitive tasks (Hermann et al., 2006). In the present study, we investigated the effect of age and cognitive decline on prefrontal brain activation during memory retrieval of temporal associated items. Temporal contiguity occurs when, presented with a list of unrelated items to learn, individuals form spontaneous temporal associations between items in order to increase retrieval. Ten younger (28.60 ± 3.24), ten cognitively healthy older (69 ± 5.3), and ten cognitively declining older (71 ± 4.40) participants completed a neuropsychological battery of tests. During the free recall task (STEM), a 12-channel fNIRS system was utilized to investigate changes in prefrontal cortical haemodynamics. There were no group differences in memory performance and temporal contiguity. Consistent with previous studies, Right medial Prefrontal Cortex (mPFC) was more active in younger adults (0.44 ± 0.21) compared to the older group (-0.95 ± 0.21), a mean difference of 1.38 (95% CI, 0.76 to 2.00), $p < .001$. Older adults showed greater activation of the left mPFC (0.13 ± 0.27) than the right (-0.95 ± 0.21), a mean difference of 1.08 (95% CI, 0.41 to 1.75), $p = .003$, whereas cognitively decliners showed no hemispheric preference. These results show that, although participants achieved comparable memory performance, older adults tended to utilize opposite neurocognitive networks to compensate for the age-related brain decline. This pattern increased in individuals with cognitive decline, as workload was added in both hemispheres. Our results suggest that right mPFC may be involved specifically in temporal contiguity, and that loss of hemispheric specialization in older adulthood may bring to compensatory strategy that activates alternative neural pathways.

Keywords: fNIRS, memory, ageing, neurodegeneration

An audit of brain tissue analysis for suspected encephalitis, with a description of the histopathological features of HSV encephalitis in acute, relapsing, and chronic disease

Harriet Van Den Tooren[1] , Nitika Rathi[2], Benedict Michael[3, 4]

1. Aintree University Hospital NHS Foundation Trust, Lower Lane, Liverpool
2. The Neuroscience Laboratory, The Walton Centre NHS Foundation Trust, Lower Lane, Liveprool
3. Institute of Infection and Global Health, University of Liverpool
4. Department of Neurology, The Walton Centre, NHS Foundation Trust, Lower Lane, Liveprool

Despite thorough clinical investigation, including cerebrospinal fluid (CSF) analysis and imaging, the aetiology of encephalitis remains unknown in a large proportion (37-63%) of cases. In these cases, investigation of brain tissue may provide the final aetiological diagnosis, allowing more directed treatment. We carried out an audit to compare the practice of brain tissue analysis for suspected encephalitis to guidance from the British Infection Association. This audit was approved by The Walton Centre Clinical Audit Group on 21st March 2018. Cases where brain tissue was analysed between January 2001 and January 2017 for suspected encephalitis were identified from the Walton Brain Biobank. Data was extracted from pathology reports and available clinical records. 31 patients were identified, and of these, eight were diagnosed as suspected or proven herpes simplex virus (HSV) encephalitis, 17 had encephalitis not attributable to HSV, and six had non-encephalitic processes. One acute case demonstrated polymerase chain reaction (PCR) and HSV immunohistochemistry positivity, one was positive for HSV immunohistochemistry without PCR testing and one was proven by demonstrating Cowdry type A inclusions without PCR or immunohistochemistry evidence of HSV. Of the six cases of proven HSV encephalitis, only three patients were able to have a lumbar puncture (LP) and CSF analysis prior to the biopsy, which were all PCR negative and HSV antibodies were not tested for. With such a range of potential aetiologies, the final diagnosis of encephalitis remains unknown for some cases even after biopsy. However, this study highlights the histopathological differences between acute, relapsing and chronic HSV encephalitis. Clinicians must remember the importance of testing for HSV using multiple methods, which include PCR and antibody testing of the CSF and culture, immunohistochemistry and PCR of tissue samples.

Keywords: Brain Biopsy, Herpes Simplex Virus, Encephalitis,

Virtual Hemianopia Treatment

Ryan Ward[1] , Abdoul Rahman, Georg Meyer

1. University of Liverpool

Hemianopia is a type of vision loss which affects both eyes in the right or left side of the visual field this can happen after a brain injury incident or a stroke. People with Hemianopia particularly have difficulty with exploration and reading tasks. Rehabilitation for patients with functional impairments and brain damage is a laborious task. Patients often undergo tedious and repetitive rehabilitation methods to help their searching ability and scan their blind side more effectively to help reduce their disability. Two novel virtual reality systems have been developed to make the process more enjoyable, less repetitive and more immersive. An HTC Vive with an integrated eye tracker has been used for accurate inpatient care and an Android/iOS application using an inexpensive head-mounted display has been developed for outpatient care. This system turns the tedious and repetitive rehabilitation, into a game, which users will look forward to playing. This game utilises searching tasks in the affected visual field with varying levels of difficulty which patients can enjoy at home.

Keywords: Hemianopia, Virtual Reality, Rehabilitation

Functional analysis of novel epilepsy mutations in STXBP1

Bangfu Zhu[1] , Alistair Jones[1], Jeff Barclay[1], Graeme Sills[2], Alan Morgan[1]

1. Institute of Translational Medicine, University of Liverpool
2. University of Liverpool

Epilepsy is a group of neurological disorders characterized by epileptic seizures. Genetics has been recognised to play an important role as some genetic variants associated with epilepsy have been identified recently. However, we now need to understand how mutations in the identified genes contribute to epilepsy and to translate this into potential therapies.

Our research has focused on STXBP1 (Syntaxin-binding protein 1) -- the second most commonly mutated gene in infantile epilepsies. STXBP1 is a member of the Sec1/Munc18 family of membrane trafficking proteins essential for neurotransmitter release. Our aims are to characterise the functional effects of disease-causing mutations in STXBP1 and to search for genetic modifiers that can ameliorate the consequences of those mutations.

In this study, we first made epilepsy-associated mutations in human STXBP1 and then generated transgenic C. elegans with each of the 8 selected mutations in STXBP1. These humanised animal models have been analysed for alterations in neurotransmission and behaviour by Thrashing Assays, and Electropharyngeogram (EPG) recordings. In the meantime, the expression levels of wild type and mutated STXBP1 were also monitored by Western blotting and qPCR.

Our data show that 3 of the mutations in STXBP1 (namely E59K, V84D and R292H) resulted in significantly defective locomotion in worms, whereas other mutants displayed little difference with wild type STXBP1/Munc18. Protein expression levels decreased dramatically in all mutants compared to wild type STXBP1/Munc18 rescue although their transcriptional expression remained at a similar level, which suggests that mutant STXBP1 proteins are destabilised after translation.

Furthermore, EPG recordings demonstrate that all 8 mutations lead to abnormal pharyngeal electric activity with a lower frequency of pumpings and irregular rhythm compared with the wild type, which implies these mutations in STXBP1 may cause epilepsy by altering electrophysiology of neurons in the brain.

Keywords: STXBP1 Mutations Epilepsy

Neurophysiological Indicators of Increased Cognitive Effort During Working Memory Examination with Modafinil Users: Findings from fNIRS and ECG

Jamie Tully[1] , Harry Sumnall[1], Stephen Fairclough[1], Catharine Montgomery[1]

1. Liverpool John Moores University

Aim: Cognitive deficits as a result of continuous illegal stimulant use are well documented. These deficits are thought to stem from dopaminergic deregulation and destruction of dopamine transporters in the brain, with use shown to also lead to adverse psychological and physical health outcomes. Moreover, studies have highlighted persistent deficits in working memory and other executive functions with prolonged stimulant use, as well as higher than average blood pressure and irregular Heart rate variability (HRV). However, despite some similarities in method of action with illegal stimulants, little is known about the long-term impact of prescription stimulants on cognitive, neurological and cardiovascular functioning. The study reported here follows on from a cross-sectional survey which identified the novel stimulant modafinil as the most popular prescription stimulant among students at 4 UK universities. This study used near-infrared spectroscopy (fNIRS) with blood pressure and ECG measurements to examine neurophysiological indicators of cognitive effort in modafinil users during tests of executive functioning.

Method: Fourteen modafinil users and 21 non-using controls completed a 3-back working memory test and a multitasking framework while prefrontal cortex haemodynamic response was measured using fNIRS. Blood pressure and HRV were also recorded with sphygmomanometer and ECG.

Results: There were no significant main effects of user group on any of the behavioural measures. Nonetheless, fNIRS showed a significant increase in Oxy-Hb on the left prefrontal cortex in users compared with nonusers on the 3-back. Within-groups analysis with sphygmomanometer and ECG revealed significant increases in systolic blood pressure and HRV between the multitasking framework difficulty conditions, but there was no significant between-groups effect or interaction apparent.

Conclusions: The absence of behavioural differences on the 3-back but significant increase in oxy-Hb in users provides evidence for the supposition that modafinil users have to invest more cognitive effort than nonusers to achieve the same results.

Keywords: fNIRS, ECG, cognitive enhancement, modafinil, cognitive effort

#LND2019