Poster number: P-W001
Theme: Attention, motivation, behaviour

Do attention and expectation act interactively or additively? - A multisensory perspective

Authors: Arianna Zuanazzi, Uta Noppeney - *School of Psychology University of Birmingham*

Attention (i.e. task relevance) and expectation (i.e. stimulus probability) are two critical determinants of perception. While attention is thought to increase the neural response to external stimuli, expectation is considered to attenuate it. Predictive coding models and recent neuroimaging research suggest that attention and expectation shape neural processing in an interactive fashion whereby attention reverses the attenuation for expected signals. Operationally, attention is often manipulated by asking participants to respond only to the 'attended' stimuli. Consequently, the synergistic effects of attention and expectation could only be evaluated at the neural level, but not at the behavioural level where 'unattended' stimuli are not responded to. This study developed a novel multisensory paradigm that allowed us to evaluate interactive effects of attention and expectation at the behavioural and neural level. In two experiments, we presented participants with auditory and visual signals in their left or right hemifields. We manipulated stimulus frequency or response requirements only to auditory signals, allowing us to measure the multisensory effects of spatial attention and expectation on behavioural responses to visual signals. Importantly, while experiment 1 manipulated expectation directly via the frequency of auditory stimuli as in (1), experiment 2 determined it indirectly via non-target stimuli that are not responded to as in (2). Our results demonstrate that the synergistic behavioural effects of attention and expectation differ across paradigms. While in experiment 1 attention and expectation influence response times interactively, in experiment 2 the two effects determine response times additively. We explain these discrepant results by a combination of overall response probability and response probabilities conditioned on the spatial hemifield where the stimulus was presented, that differ across the two paradigms. Response times reflect response probability determined by the specific manipulation employed. Concurrent fMRI experiments investigate the neural mechanisms underlying these multisensory effects of attention and expectation.

(1)Kok et al.(2012) doi.org/10.1093/cercor/bhr310
(2)Jiang et al.(2013) doi.org/10.1523/JNEUROSCI.3308-13.2013

Contact email address: axz481@bham.ac.uk

Poster number: P-W002
Theme: Attention, motivation, behaviour

Trait impulsivity in rats is associated with reduced myoinositol in the infralimbic cortex

Authors: Bianca Jupp, Suzanne Lemstra, Bas Van Der Veen, Steve Sawiak, Rebecca Barlow - *Psychology Cambridge University*, Anton Pekcec - *CNS Discovery Support Boehringer Ingelheim*, Tom Bretschneider - *Drug Discovery Support Boehringer Ingelheim*, Janet Nicholson - *CNS Discovery Support Boehringer Ingelheim*, Trevor Robbins, Jeffrey Dalley - *Psychology Cambridge University*

Impulsivity is defined as a tendency for premature, unduly risky and poorly conceived actions and as a behavioural trait is associated with a number of psychiatric disorders including attention deficit/hyperactivity disorder (ADHD) and bipolar disorder, and is thought to involve dysfunction within cortico-striatal circuitries. Here we investigate the putative metabolic cortico-striatal correlates of impulsivity using in-vivo proton magnetic resonance spectroscopy (1H MRS) in rats selected on the basis of expression of innately high or low levels of premature responding on the five choice serial reaction time task (5CSRTT). High impulsive rats demonstrated significantly reduced prefrontal cortical levels of myoinositol, a metabolite associated with the inositol triphosphate/calcium (IP3/Ca2+) signalling cascade. No other differences in metabolite concentrations were observed between high and low impulsive animals in either the prefrontal cortex or striatum. Ex-vivo mass spectroscopy examining myoinositol levels in individual sub-regions of the prefrontal cortex in an independent group of animals confirmed a reduction in myoinositol levels in high impulsive rats, specifically within the infralimbic cortex. To further investigate the ontology of this metabolic dysfunction, we examined transcript levels of a number of key enzymes and proteins involved in the metabolism and cellular transport of myoinositol and its precursors within the infralimbic cortex. Significant reductions in transcript levels were observed for the enzyme inositol monophosphate synthanse 1 (IMPase1) and the sodium inositol co-transporter (SMIT1) in high impulsive rats compared with low impulsive rats. The main findings of this study suggest that trait impulsivity in rats is associated with reductions in the level of myoinositol in the infralimbic cortex, potentially driven by reductions in the capacity for intracellular transport and calcium signalling.
Contact email address: bj251@cam.ac.uk

Poster number: P-W003
Theme: Attention, motivation, behaviour

Visual imagery: the experience of aphantasia and hyperphantasia

Authors: Crawford Winlove, James Gaddum, Brittany Heuerman-Williamson, Adam Zema - *Medical School University of Exeter*

AIM
Imagination - the ability to call to mind things that are not present to the senses - allows us to explore the past, the future, and the potentially possible. For most people, visual imagery is a conspicuous element of imagination, but some people report its absence. We have called this absence of visual imagery aphantasia. Here, we present preliminary data from a large questionnaire survey of individuals whose imagery falls at the extremes of the vividness spectrum.

METHOD
2,012 members of our user group completed a Visual Imagery Questionnaire, (VVIQ, Marks 1973), a widely-accepted measure of mental imagery. Participants scoring between 16 and 24 on the VVIQ, were classified as aphantasic; those scoring >77 were classified as hyperphantasic. Their employment was categorised using Standard Occupational Classification (US Department of Labor, 2000).

RESULTS
We focus here on individuals with lifelong aphantasia or hyperphantasia who comprised the overwhelming majority of participants. 19% of people with aphantasia worked in computer and mathematical occupations; only 8% of people with hyperphantasia reported working in these fields. Amongst those with vivid imagery, 29% worked in the Arts, Design, Entertainment, Sports, and Media Occupations, compared to 13% of people with aphantasia. A family history in first degree relatives of aphantasia and hyperphantasia was obtained in 15-20% of participants. The majority of participants with aphantasia (70%) experience imagery in dreams. Roughly equal numbers of participants with aphantasia reported the presence and absence of imagery in other modalities. Face recognition difficulties were reported commonly by participants with aphantasia (35%). More individuals with aphantasia (34%) than hyperphantasia (5%) regarded their autobiographical memory as poor; conversely 23% of people with hyperphantasia compared to 8% of people with aphantasia regarded their autobiographical memory as good.

CONCLUSIONS
Preliminary data from this large sample of individuals falling at the extremes of the imagery spectrum suggests that imagery vividness is a lifelong trait. Low imagery vividness appears to be overrepresented among people working in IT related and mathematical domains, high vividness among those working in
Contact email address: c.i.p.winlove@exeter.ac.uk

Poster number: P-W004
Theme: Attention, motivation, behaviour

Categorical differences in the conscious access to visual objects

Authors: Daniel Lindh - *School of psychology University of Birmingham*

The ability to consciously recognise visual objects is crucial for adaptive behaviour and survival. Conscious access to visual objects has been studied using the Attentional Blink (AB), where two targets (T1 and T2) are embedded with visual masks in a rapid serial visual presentation (RSVP). In the AB, the ability to detect T2 is reduced when presented 200-500ms post T1. Research using functional Magnetic Resonance Imaging (fMRI) has proven useful to identify the underlying brain mechanisms of conscious access. Given the challenges inherent to the limited temporal resolution of fMRI, researchers have designed AB-studies in which T1 and T2 targets are selected from image categories known to engage different regions in the visual stream. However, to integrate these findings into a consistent model of conscious access, the variability in detection thresholds across categories needs to be assessed. Specifically, we investigated the categorical differences in conscious and unconscious processing using a behavioural attentional blink task. Here, we presented participants with 48 pictures of objects from eight categories (fruits and vegetables, processed foods, objects, scenes, animal bodies, animal faces, human bodies, and human faces) in an AB-task (Fig. 1A). Each picture was presented as T1, and at two different T2-lags (200ms and 700ms post T1). To compare the performance at recalling target objects across categories, we used a factorial ANOVA with performance effect of T2-lag and object category as factors (Fig. 1B). We observed main effects of T2-lag ($F(1,20)=51.47$, $p < 0.001$) and category ($F(7,140)=51.6$, $p < 0.001$), along with an interaction between category and T2-lag ($F(7, 140)=27.4$, $p < 0.001$). Beyond the expected AB effect, this means that different object categories exhibit different detection thresholds. We further pooled the objects according to animate and inanimate categories, which are known to vary in their processing

speeds. Here, a pairwise t-test revealed a markedly smaller AB-magnitude for animate objects (t=4.5199, df=37.297, p < 0.001). These findings indicate a behavioural advantage for animate objects in their representational readouts, advocating for careful consideration of stimulus materials in conscious access research.

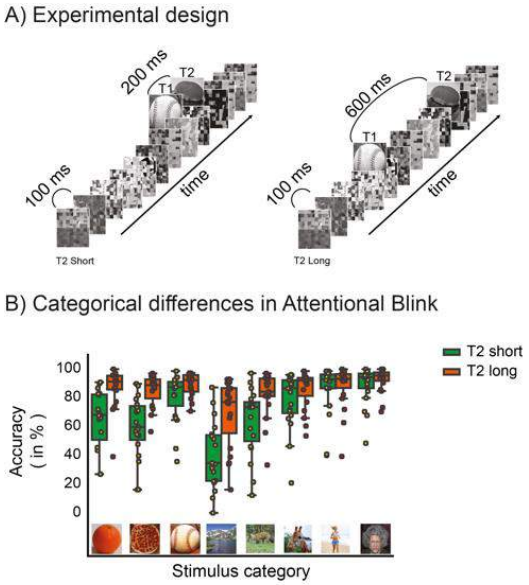


Figure 1: General design and main results.
(A) Schematic representation of the experimental design. Subjects viewed a rapid serial visual presentation (RSVP) constituting of two targets (T1 and T2) embedded in temporally surrounding masks. The order of the two conditions (T2 short and T2 long) was randomized within each block. (B) Main behavioural results. Average accuracy score per category (fruits & vegetables, processed foods, objects, scenes, animal bodies, animal faces, human bodies, human faces), where T2 short and T2 long trials are depicted in green and orange boxes, respectively. The scatter plot indicates individual performance over the different categories and conditions. A 2x8 ANOVA (T2 Long/Short X Category) revealed main effects of T2 lag and T2 category as well an interaction. These results indicate categorical differences on attentional blink magnitude.

Contact email address: dnllndh@gmail.com

Poster number: P-W005
Theme: Attention, motivation, behaviour

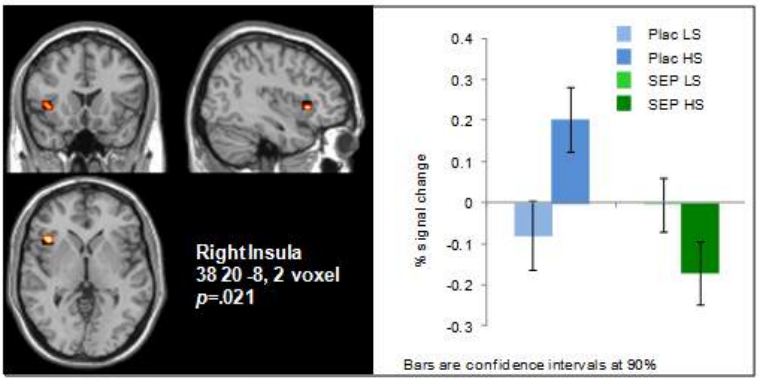
A phase 1 functional neuroimaging study of a new compound in healthy volunteers with high or low schizotypy

Authors: Jadwiga Nazimek, Francesca Perini, Shane McKie - *Division of Neuroscience and Experimental Psychology University of Manchester*, Mike Browning, Gerry Dawson - *P1vital P1vital*, Nishikawa H, Campbell U, Hopkins S, Loebel A, Koblan K - *Sunovion Pharmaceuticals Inc. Marlborough MA, USA*, Bill Deakin - *Division of Neuroscience and Experimental Psychology University of Manchester*

BACKGROUND: SEP-363856-363856 is a novel compound effective in animal models of schizophrenia and depression, but without D2 or 5-HT2A receptor activity. It may act through 5 HT1A and TAAR1 receptors. This study evaluated the potential for antipsychotic/antidepressant-like effects on reward- and emotional-processing of SEP-363856.
METHODS: 96 healthy volunteers with high (HS) or low schizotypy (LS) scores were randomized to SEP-363856, amisulpride or placebo. Functional magnetic resonance imaging blood oxygen level dependent (BOLD) signals in brain regions of interest were measured during Monetary Incentive Delay (MID), N-back task and resting state connectivity (RSC). The antidepressant-like effects of SEP-363856 were assessed with P1vital Oxford Emotional Testing Battery (ETB).
RESULTS: MID. Reward anticipation activated ventral striatum and deactivated medial orbitofrontal cortex (mOFC). HS was associated with insula activations relative to deactivations in LS. Compared with placebo, SEP-363856 decreased striatal and induced mOFC activation. SEP-363856 prevented insula activation in HS in anticipation of loss (FWE p=0.02). The pattern of effects of SEP-363856 on activity in striatum and insula resembled amisulpride's profile. In outcome phase SEP-363856 enhanced activation

to win and loss compared to amisulpride in the left insula. RSC. HS participants had significantly reduced default mode (DMN), salience (SN) and right executive control network connectivity compared to LS. Both drugs reduced effect of schizotypy, amisulpride significantly in DMN and SEP-363856 in SN (anterior insula, FWE p=0.0026). N-back. Neither drug nor HS modified activations in the dorsolateral prefrontal cortex. ETB. Compared to placebo, SEP-363856 reduced performance independently of valence. The pattern of effects of SEP-363856 was similar to amisulpride, and different from reference antidepressants.
DISCUSSION: SEP-363856 effects in striatum, mOFC and insula in the MID suggest its novel effects on dopamine function influence hedonic processes with no effect on emotion processing in the ETB. These findings together with its reversal of the effect of HS in insula on the MID and RSC measures point to potential therapeutic benefits of SEP-363856-363856 in psychotic disorders.

Figure 9.1.4.1. Interaction of schizotypy with treatment (placebo vs SEP-363856) in the anticipation phase contrast loss vs neutral the right insula.



HS = high schizotype, LS = low schizotype, Plac = placebo, SEP = SEP-363856. Bars represent standard error of the mean, $p<0.05$ (corrected).

Contact email address: jadwiga.nazimek@manchester.ac.uk

Poster number: P-W006
Theme: Attention, motivation, behaviour

The neural underpinnings of willingness-to-pay: an event-related potential study.

Authors: John Tyson-Carr, Katerina Kokmotou, Vicente Soto, Stephanie Cook - *Psychology University of Liverpool*, Timo Giesbrecht - *Research and Development Unilever,* Andrej Stancak - *Psychology University of Liverpool*

The value of environmental cues and internal states are continuously evaluated by the human brain, either consciously or sub-consciously. Ultimately, it is this subjective value that guides the decision making process. The present study aimed to investigate the spatio-temporal aspects of brain economic valuation using electroencephalography.

Participants completed a stimulus rating task in which decisions where either value-relevant (desirability) or -irrelevant (material estimation). Willingness-to-pay (WTP) values were used as a measure of subjective economic value for the stimuli, obtained using the Becker-DeGroot-Marschak (BDM) auction. The stimulus set comprised everyday household items valued up to £4, split into high and low value based on subjective WTP values. A sequential strategy was used to examine value-induced modulation of event-related potential responses to stimulus presentation.

Source dipole reconstruction highlighted the role of the right anterior insula cortex, left orbitofrontal cortex, right parahippocampal gyrus and the posterior cingulate cortex in these economic decisions relating to WTP. Source activity was greater in the right anterior insular cortex and the right parahippocampal gyrus for the desirability rating condition than for the material estimation condition. Source activity was also greater for low value items than for high value items in the right anterior insula and the left orbitofrontal cortex. These effects were all observed within the latency of the P2 and N2 component at approximately 200ms.

Findings suggest a negativity bias towards low value items, possibly due to the low value items presenting a source of potential financial loss. The insula is well established as being the centre for risk and loss aversion and could potentially explain this finding. The importance of the right anterior insular cortex and the right parahippocampal gyrus in economic decisions is apparent with facilitated source activity in these regions when value was relevant.

Contact email address: hljtyson@liverpool.ac.uk

Poster number: P-W007
Theme: Attention, motivation, behaviour

Contrasting effects of dopamine and serotonin manipulations on action initiation, selection and inhibition

Authors: Laura Grima, Oliver Harmson - *Experimental Psychology University of Oxford*, Emilie Syed - *MRC Brain Network Dynamics Unit University of Oxford*, Masud Husain - *Experimental Psychology; Nuffield Department of Clinical Neurosciences University of Oxford*, Mark Walton - *Experimental Psychology University of Oxford*

Dopamine and serotonin neurotransmission are key, possibly antagonistic and interacting, modulators of reward-guided behaviour. There is evidence that dysfunction in either system can result in impulsive choice. However, their precise roles in action initiation and inhibition remain unclear, particularly in the context of switching between initiating or withholding goal-directed movement for reward.

To this aim, we employed a task where cues instructed rats either to make ('Go') or withhold ('No-Go') an action to gain a large or small reward. In a first experiment, we pharmacologically manipulated dopamine transmission using either a D1 antagonist (SCH 23390) or agonist (SKF 81297), or a D2 antagonist (eticlopride) or agonist (quinpirole), applied in a within-subjects counterbalanced design. Stimulation of D1 receptors caused a reward-dependent increase in inappropriate, impulsive actions on No-Go trials, particularly immediately after cue presentation. By contrast, both stimulation of D1 or D2 receptors reduced correct Go responses, though for different reasons: while D2 receptor stimulation increased the number of missed trials, D1 receptor stimulation increased incorrect selection of the large reward 'Go' option on trials when the cue instructed a small reward response.
In a second experiment, we investigated the role of 5-HT neurotransmission in the same task using a 5-HT2C receptor-selective ligand, SB242084, which is known to influence dopamine neuron activity and dopamine release. As with stimulation of D1 receptors, this manipulation also reduced rats' ability to withhold movement for reward on No-Go trials. However, in contrast to dopamine manipulation, actions became more likely the longer it had been since cue presentation. Moreover, SB242084 increased accuracy and decreased response latencies on Go trials, thereby breaking the speed-accuracy trade-off.
In summary, while imbalance in either dopamine or serotonin transmission can cause an increase in impulsive actions, the underlying mechanisms may be different. Specifically, while D1 transmission influences how cues are used to promote and direct actions, 5-HT2C transmission shapes instrumental drive and response precision.

Contact email address: laura.grima@psy.ox.ac.uk

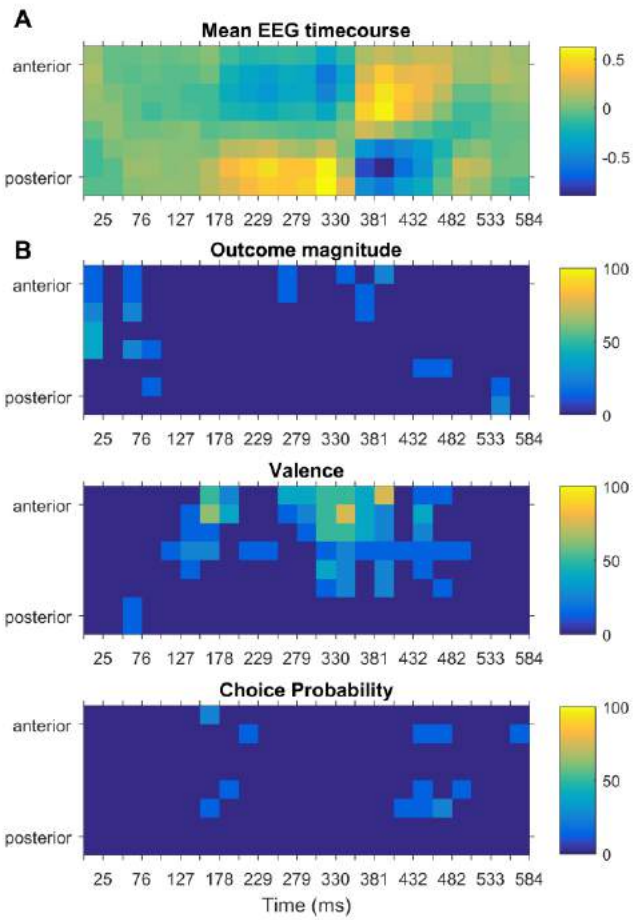
Poster number: P-W008
Theme: Attention, motivation, behaviour

Computational EEG Modelling of Decision Making Under Ambiguity Reveals Spatio-Temporal Dynamics of Outcome Evaluation

Authors: Lee Jollans, Robert Whelan - *School of Psychology Trinity College Dublin*, Louise Venables - *Department of Psychology Swansea University*, Oliver H. Turnbull - *School of Psychology Bangor University*, Matteo Cella, Simon Dymond - *Department of Psycholoy Swansea University*

Complex human cognition, such as decision-making under ambiguity, is reflected in dynamic spatiotemporal activity in the brain. Here, we evaluated decision-making in a population of healthy adults (n=20), using EEG and computational modelling of task choices in the Iowa Gambling Task (IGT). In the IGT participants choose among four decks of cards which yield different average hypothetical monetary win and loss. The participants' goal is to maximize profit. We combined a computational model of decision-making behaviour in the IGT with EEG to examine the brain-correlates of ostensibly subjective choice evaluation components. We used the Prospect Valence Learning Delta (PVL-Delta) model to generate measures of choice probability, which were applied as regressors in a general linear model of the EEG signal alongside objective trial outcomes (outcome magnitude and valence). The resulting three-dimensional spatiotemporal characterization of task-related neural dynamics demonstrated that outcome valence, outcome magnitude, and PVL-Delta choice probability were expressed in distinctly separate event related potentials, with surprisingly little overlap between the spatiotemporal characterizations of the regressors. We found that outcome magnitude and valence were both strongly correlated with two event-related potentials (ERPs) which are well established components of outcome processing: the Feedback related negativity (FRN), and the P300 potential. While past research has indicated that P300 shows a stronger association with magnitude than the FRN, and that valence shows the opposite pattern, our findings suggest that this distinction may not be as definitive as previously thought. Furthermore, our findings showed that P300 was associated with the ostensibly subjective and experience-based measure of outcome expectancy generated using the PVL-Delta model. This is in line with previous research that has found associations between P300 and subjective outcome expectation components. Our findings support a theory of P300 as reflecting decision formation, incorporating awareness of a mistake having been made. Future research

could benefit from using a larger sample, and utilizing a money-earning variant of the IGT rather than the hypothetical rewards used in this study.



(A) ERPs in each temporal bin from anterior to posterior, averaged over left and right. (B) Percentage of spatial bins from left to right in which each regressor (outcome magnitude, valence, and choice probability) was significantly associated with the ERP in each time bin at each of eight spatial locations from anterior to posterior.

Contact email address: ljollans@tcd.ie

Poster number: P-W009
Theme: Attention, motivation, behaviour

The effects of LSD on music-evoked brain activity and emotion

Authors: Mendel Kaelen - *Medicine Imperial College London*

Psychedelic drugs such as lysergic acid diethylamide (LSD) activate the serotonin 2A receptor (Titeler et al., 1988) and produce marked reductions in functional coupling within high-level brain networks (Carhart-Harris et al., 2016), and simultaneous increased cross-talk between low-level areas (Tagliazucchi et al., 2016). This network "collapse" is argued to underlie psychedelics' subjective effects (Carhart-Harris et al., 2014), that include intensified music-evoked emotion (Kaelen et al., 2015). The aim of this study was to investigate the acute effects of LSD on music-evoked brain-activity under naturalistic music listening conditions, and to relate these changes in brain function with changes in music-evoked emotion. 16 healthy participants were enrolled in magnetic resonance imaging (fMRI) while listening to a 7 minute music piece under eyes-closed conditions on two separate visits (LSD (75 mcg) and placebo). Music-evoked emotion was measured with the Geneva Emotional Music Scale. Inspired by recent work (Alluri et al., 2012; Burunat et al., 2016), 23 acoustic features were extracted from the two excerpts, and underwent principle component analysis (PCA) to reduce dimensionality. Timecourses of the first 8 principal components (PC's, >90% of variance) were entered into subject-level fMRI analyses as regressors of interest. Resulting individual subject-level contrasts were entered into high-level analyses to obtain paired t-test contrasts of LSD>Placebo and Placebo<LSD. The study revealed altered brain activity and functional connectivity to acoustic features in music under LSD. Most pronounced changes were observed for the component timbral complexity, representing the complexity of the music's spectral distribution. These occurred in brain networks previously identified

for music-perception and music-evoked emotion (Trost et al., 2012), including inferior frontal gyrus, planum temporale and superior temporal gyrus, and showed an association with enhanced music-evoked feelings of wonder. The findings are the first to shed light on how the brain processes music's acoustic features under LSD, and improve out understanding on brain processes underlying music perception and emotion under naturalistic listening conditions.
Contact email address: m.kaelen@imperial.ac.uk

Poster number: P-W010
Theme: Attention, motivation, behaviour

Neural correlates of loneliness explain the relationship between social support and depressiveness

Authors: Nichol M. L. Wong - *Laboratory of Neuropsychology The University of Hong Kong*, Jingsong Wu - *Rehabilitation Medicine College Fujian University of Traditional Chinese Medicine*, Xiujuan Geng - *Laboratory of Neuropsychology The University of Hong Kong*, Jing Tao - *Rehabilitation Medicine College Fujian University of Traditional Chinese Medicine*, Chetwyn C. H. Chan - *Applied Cognitive Science Laboratory The Hong Kong Polytechnic University*, Lidian Chen - *Fujian University of Traditional Chinese Medicine,* Tatia M. C. Lee - *Laboratory of Neuropsychology The University of Hong Kong*

Less adequate social support can predict later depressiveness with perceived loneliness significantly contributing to depression. Specifically, social support can be categorised into different types and perceived loneliness appears to have three different dimensions, including emotional (intimate) and social (relational) loneliness. Therefore, this study investigates how different dimensions of loneliness can explain the relationship between social support and depressiveness.
Ninety-four healthy subjects ranging from 15 to 70 years of age are included in this study. Subjects' objective support, subjective support and utilization of social support were captured. Their perceived loneliness were measured in three dimensions, namely the intimate loneliness, relational loneliness, and collective loneliness. Subjects' depressiveness were also measured. Structural and diffusion MRI data were acquired. Voxel-based morphometry and tract-based spatial statistics were applied on grey matter volume and fractional anisotropy of white matter respectively to identify the neural correlates of social support, loneliness and depressiveness.

From apriori hypotheses and correlational findings, a path model is established with dimensions of loneliness explaining the prediction of social support on subjects' depressiveness, of which intimate loneliness is crucial (Figure 1A). From the MRI analyses, loneliness did not correlate with the grey matter volume; with intimate and collective loneliness negatively associated with the fractional anisotropy of major white matter tracts (Figure 1B). Specifically, as per the subjective-support-intimate-loneliness-depressiveness path, fractional anisotropy of the overlapping white matter correlates of subjective social support and intimate loneliness were negatively related to depressiveness (Figure 1C).

It is concluded that intimate loneliness mainly explains the relationship between subjective social support and depressiveness with a neuobiological basis, providing insights in treating psychosocial disorders.

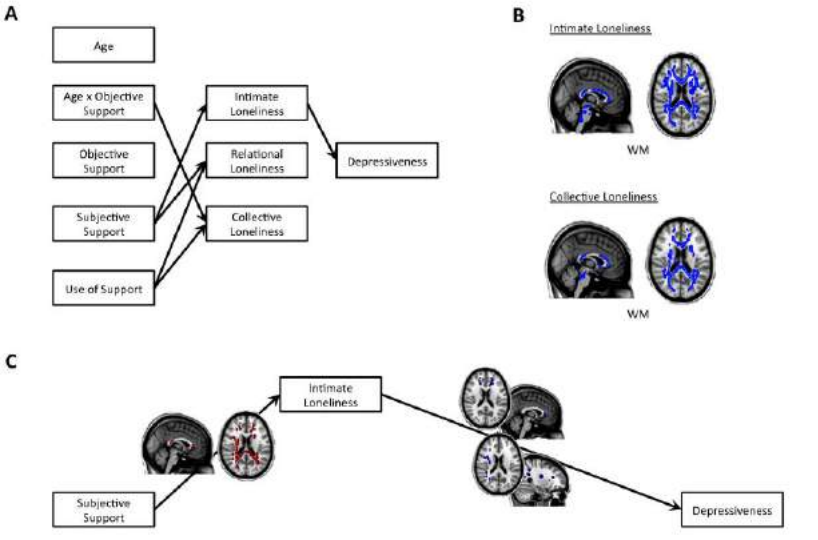


Figure 1. (A) The significant paths of how loneliness explains the relationship between social support and depressiveness are shown. (B) Based on structural and diffusion MRI, intimate and collective loneliness are negatively related to fractional anisotropy across major tracts. (C) Fractional anisotropy of overlapping neural correlates of subjective social support and intimate loneliness are negatively associated with depressiveness.

Contact email address: nmlwong@hku.hk

Poster number: P-W011
Theme: Attention, motivation, behaviour

Chemogenetic Activation of Melanopsin Retinal Ganglion Cells Induces Signatures of Arousal and/or Anxiety in Mice

Authors: Nina Milosavljevic, Jasmina Cehajic-Kapetanovic, Christopher A. Procyk, Robert J. Lucas - *Faculty of Biology, Medicine and Health The University of Manchester*

Functional imaging and psychometric assessments indicate that bright light can enhance mood, attention, and cognitive performance in humans. Indirect evidence links these events to light detection by intrinsically photosensitive melanopsin-expressing retinal ganglion cells (mRGCs). However, there is currently no direct demonstration that mRGCs can have such an immediate effect on mood or behavioural state in any species. We addressed this deficit by using chemogenetics to selectively activate mRGCs, simulating the excitatory effects of bright light on this cell type in dark-housed mice. This specific manipulation evoked circadian phase resetting and pupil constriction (known consequences of mRGC activation). It also induced c-Fos (a marker of neuronal activation) in multiple nuclei in the hypothalamus (paraventricular, dorsomedial, and lateral hypothalamus), thalamus (paraventricular and centromedian thalamus), and limbic system (amygdala and nucleus accumbens).

These regions influence numerous aspects of autonomic and neuroendocrine activity and are typically active during periods of wakefulness or arousal. By contrast, c-Fos was absent from the ventrolateral preoptic area (active during sleep). In standard behavioural tests (open field and elevated plus maze), mRGC activation induced behaviours commonly interpreted as anxiety like or as signs of increased alertness. Similar changes in behaviour could be induced by bright light in wild-type and rodless and coneless mice, but not melanopsin knockout mice. These data demonstrate that mRGCs drive a light-dependent switch in behavioural motivation toward a more alert, risk-averse state. They also highlight the ability of this small fraction of retinal ganglion cells to realign activity in brain regions defining widespread aspects of physiology and behaviour.
Milosavljevic N, Cehajic-Kapetanovic J, Procyk CA, Lucas RJ. Chemogenetic Activation of Melanopsin Retinal Ganglion Cells Induces Signatures of Arousal and/or Anxiety in Mice. Curr Biol. 2016; 26:2358-63.

Contact email address: nina.milosavljevic@manchester.ac.uk

Poster number: P-W012
Theme: Attention, motivation, behaviour

Investigating the effect of individual housing on male mice behaviour.

Authors: Oda Moe Sorensen - *Physiology, Pharmacology and Neuroscience University of Bristol*

A persistent problem in the field of laboratory animal welfare is the development of aggressive behaviour, particularly in mice. Not only can these behaviours lead to wounding, pain and suffering of the animal, but they can also induce altered physiology that may affect data variability and the scientific validity of the study. The most common solution is to house mice individually, but there is concern as to whether this creates new behavioural issues. In this study we investigated whether prolonged individual housing of mice causes behavioural changes that may be indicative of reduce welfare. 16 male CD1 mice (~16g) were housed either in individual cages (n=8), or in groups of 4 (n=8) for 4 weeks prior to behavioural testing. A behavioural screen was used to assess a number of active and static behaviours on a weekly basis for 6 weeks. Sampling was carried out under two conditions each week: control conditions vs a mild stressor (routine cage-cleaning). A novelty suppressed feeding test (NSFT) was carried out at the end of the study to assess anxiety-related behaviour. Our results showed that mice housed individually developed a more static behavioural profile under habituated conditions over the study period, resulting in a significant difference from group housed animals in the last two weeks of testing. Individually housed mice also demonstrated significantly more exploratory behaviours on cage-cleaning days than group-housed animals. Overall there was a greater tendency for individually housed animals to develop stereotypic behaviours during the study. In the NSFT, individually housed animals showed a faster approach latency but slower feeding latency than group housed animals. These data indicate that mice housed individually may develop general signs of negative affect, as well as anxiety-related behaviours in response to novel environments. This suggests that individual housing of laboratory animals presents a welfare concern and there is a need to find alternative measures to reduce aggressive behaviours in group housed animals.

Contact email address: os12568@bristol.ac.uk

Poster number: P-W013
Theme: Attention, motivation, behaviour

Perseveration in spatial-discrimination reversal learning is differentially affected by MAO-A and MAO-B inhibition and associated with reduced anxiety

Authors: Peter Zhukovsky, Johan Alsioe, Bianca Jupp, Jing Xia, Chiara Giuliano, Angela Roberts, Trevor Robbins, Jeffrey Dalley - *Psychology, University of Cambridge*

Rationale: Impairments in behavioural flexibility lie at the core of anxiety and obsessive-compulsive disorders. Few studies, however, have investigated the neural substrates of natural variation in behavioural flexibility and whether inflexible behaviour is linked to anxiety and peripheral markers of stress and monoamine function.

Objectives: To investigate peripheral and central markers associated with perseverative behaviour on a spatial-discrimination serial reversal-learning task.

Methods: Rats were trained on a reversal-learning task prior to blood sampling, anxiety assessment, and the behavioural evaluation of selective monoamine oxidase-A (MAO-A) and MAO-B inhibitors, which block the degradation of serotonin (5-HT), dopamine (DA) and noradrenaline (NA).

Results: Perseveration correlated positively with 5-HT levels in blood plasma, and inversely with trait anxiety, as measured on the elevated plus maze. No significant relationships were found between perseveration and the stress hormone corticosterone or the 5-HT precursor tryptophan. Reversal learning was significantly improved by systemic administration of the MAO-A inhibitor moclobemide but not by the MAO-B inhibitor lazabemide. Moclobemide also increased latencies to initiate a new trial following an incorrect response suggesting a possible role in modulating behavioural inhibition to negative feedback. MAO-A but not MAO-B inhibition resulted in pronounced increases in 5-HT and NA content in the orbitofrontal cortex and dorsal raphé nuclei, and increased 5-HT and DA content in the basolateral amygdala and dorsomedial striatum.

Conclusions: These findings indicate that central and peripheral monoaminergic mechanisms underlie inter-individual variation in behavioural flexibility, which overlap with trait anxiety and depend on functional MAO-A activity.

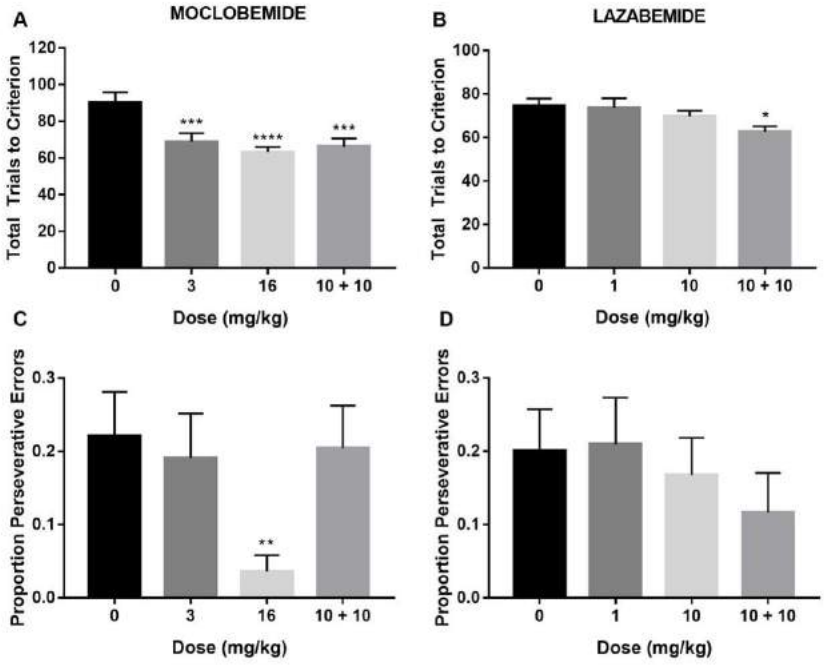


Figure 4. Effects of moclobemide (n=18) and lazabemide (n=21) on total trials to achieve criterion (**A, B**) and the proportion of perseverative errors (**C, D**). Mean values ± SEM for a single post-drug administration session are shown. Significance is denoted as follows: *p<0.05, **p<0.01, ***p<0.001 versus vehicle.

Contact email address: pz249@cam.ac.uk

Poster number: P-W014
Theme: Attention, motivation, behaviour

Acute selective serotonin reuptake inhibition, but not 5HT2C receptor antagonism, impairs conditioned fear and safety signal expression

Authors: Polyvios Theodotou, Trevor William Robbins - *Department of Psychology University of Cambridge*

Safety signals are cues that predict the non-occurrence of aversive outcomes. They represent a specific variant of conditioned inhibition, insofar they reduce fear responses (e.g., freezing) upon presentation and are detected using summation and retardation tests. Thus, Pavlovian conditioned inhibition of fear (or learned safety) can be conceptualized as a learning process protecting against chronic stress, a predisposing factor for various psychopathologies. Conversely, serotonin release is triggered in response to stress, especially in key brain regions driving fear conditioning and expression. Whilst selective serotonin reuptake inhibitors (SSRIs) can effectively treat affective and anxiety disorders, they also produce anxiogenic effects prior to their clinical action (i.e., activation syndrome). Here, we report that an acute dose (i.p.) of the SSRI, escitalopram, leads to enhanced fear extinction and impaired safety signalling expression in naïve rats. We also show that the selective 5HT2C receptor antagonist, SB242084, neither consistently improves nor impairs acquisition and expression of safety in naïve rats but does exert baseline dependent effects on freezing behaviour. We conclude that enhanced global serotonin efflux during initial treatment with SSRIs may impair newly acquired inhibitory associations while inducing perseveration of excitatory ones.

Contact email address: theodotou1989@gmail.com

Poster number: P-W015
Theme: Attention, motivation, behaviour

An fMRI assessment for test-retest reliability of task switching in healthy adults

Authors: Rong Ye, Leon Aksman, Anna Combes, Angie A. Kehagia, Mitul A. Mehta - *Department of Neuroimaging Institute of Psychiatry, Psychology and Neuroscience*

Background:
Task switching paradigms are widely used to index cognitive flexibility. In clinical research, task performance can be used to monitor disease progression or to evaluate the effectiveness of interventions. Good test-retest reliability is required to determine the sensitivity of such studies and contribute to the interpretation of changes over time, or following interventions. Here, we sought to determine the stability of performance and brain activations using an fMRI task.

Methods:
Fourteen older healthy subjects were scanned in three sessions while performing a switching task (age: 60.5±7.8 yo; time intervals from the 1st scan: 5.8±2.0, 28.1±5.2 days for the 2nd and the 3rd scan respectively). A multivariate pattern classification was adopted for imaging data analysis given that this approach may be more appropriate for our task switching paradigm (Kehagia et al., unpublished). Imaging data were pre-processed and modelled in SPM12. Beta images for both repeat and switch conditions were subsequently submitted in pattern analyses. Classifiers for the first two sessions were evaluated and used for categorical predictions on the following ones using customised Matlab scripts and functions from PRoNTo. Medians of the third intraclass-correlation coefficient (ICC) for both behavioural and image data were calculated in a locally developed toolbox for the reliability assessments (Caceres et al., 2009).

Results:
Prominent switch costs were observed for all sessions and this behavioural index has good overall reliability (ICC=0.69) with the highest ICC for sessions 2 and 3 (ICC=0.80). The highest reliability of classification probability was also found between the last two sessions for differentiating brain networks involving in repeat and switch conditions (ICC=0.60). Scans acquired from the 1st session showed poor ability for reliably classifying conditions at the 2nd (ICC=0.39) and the 3rd (ICC=0.33) time point.

Conclusion:
We concluded that behavioural performance and brain activation pattern were highly consistent at the time-point two and three. When using the task switching paradigm repeatedly, an initial full-length training session is recommended in order to achieve a stable level of performance.

Contact email address: rong.ye@kcl.ac.uk

Poster number: P-W016
Theme: Attention, motivation, behaviour

Disruption of oral somatosensory relay, but not taste sensory, may increase depression-like behaviors in rats

Authors: Sena Chung - *Dental Science Seoul National University School of Dentistry*, Doyun Kim - *Oral & Maxillofacial Surgery Seoul National University Dental Hospital*, Jong-Ho Lee - *Dental Science Seoul National University School of Dentistry*, Jeong Won Jahng - *Dental Research Institute Dental Research Institute*

We have previously reported that bilateral transection of the lingual and chorda tympani nerves (Nx) results in behavioral depression in rats. Anhedonia, a core symptom of depression, can be easily measured by decreased consumption of sweet solutions in rodent models. Sucrose consumption was significantly reduced in Nx rats compared to sham operated controls, revealing anhedonic feature of Nx-induced depression. This study was conducted to examine if Nx-induced depression is mainly due to the loss of chorda tympani (taste) nerves rather than the loss of lingual (somatosensory) nerves. After a week of post-operational recovery from the bilateral transection of chorda tympani nerves (CTx) or Nx surgery, rats were subjected to a three-bottle preference test (one sucrose and two water bottles) daily for 9 consecutive days, and then to forced swim test. Nx rats did not prefer to drink sucrose during the whole experimental period. However, CTx rats drank more sucrose than water during the whole test period, although sucrose intake was reduced in CTx rats compared to sham rats during the first two days of the test. Immobility during the swim test was increased in Nx, but not in CTx, compared to sham rats. Stress-induced corticosterone increases did not differ among the experimental groups. Neuronal activities in the nucleus accumbens are currently under investigation. Results suggest that disruption of oral somatosensory, but not taste sensory, relay from the anterior two thirds of the tongue may induce depression with anhedonic feature, and the stress-axis function may not be involved in its underlying mechanism.
Supported by a grant from National Research Foundation of Korea through the Oromaxillofacial Dysfunction Research Center for the Elderly (2015048003) at Seoul National University in Korea.

Contact email address: s_e_na@snu.ac.kr

Poster number: P-W017
Theme: Attention, motivation, behaviour

Functional characterization of Leda-1/Pianp in the murine nervous system

Authors: Siladitta Biswas - *Klinik für Dermatologie, Venerologie und Allergologie*, *Universitätsmedizin Mannheim University of Heidelberg*, Stefan Berger - *Zentralinstitut für Seelische Gesundheit, Molecular Biology University of Heidelberg*, Manuel Winkler - *Klinik für Dermatologie*, *Venerologie und Allergologie, Universitätsmedizin Mannheim University of Heidelberg*, Dorde Komljenovic - *Medical Physics in Radiology, Molecular Imaging DKFZ, Heidelberg*, Dusan Bartsch - *Zentralinstitut für Seelische Gesundheit, Molecular Biology University of Heidelberg*, Cyrill Géraud - *Klinik für Dermatologie, Venerologie und Allergologie, Universitätsmedizin Mannheim University of Heidelberg*

Introduction
Leda-1/Pianp is a type-I transmembrane protein initially identified in rat liver endothelium. The Leda-1/Pianp protein is highly conserved among mammals. Transcript analysis and western blotting revealed the highest expression levels of Leda-1/Pianp in the CNS of human, rats and mice. Expression is also found in human astrocytes, glioblastoma cell lines and BALB/c but not C57BL6/J mice lymphoid organs (lymph node, spleen and thymus). The protein is glycosylated and undergoes multiple steps of proteolytic processing. Its N-terminus is cleaved by pro-protein convertases like Furin, ADAMs, MMPs. Subsequently the y-secretase complex cleaves it intramembraneously. The only known interaction partner of Leda-1/Pianp is the immune inhibitory receptor PILRa. However the function of Leda-1/Pianp in the CNS is so far not characterized.

Aim
Characterization of Leda-1/Pianp expression in different brain regions and behavioral phenotyping of Leda-1/Pianp knock out mice.

Methods
Expression analysis of mouse brain subregions by quantitative western blotting. Behavioral tests to assess locomotor activity, stress resisting behavior, anxiety like behavior, delayed fear conditioning and sociability of Leda-1/Pianp knock out mice.

Results & conclusion
Leda-1/Pianp-/- mice were viable. Also body weight and plasma lab values were comparable to wild type mice. CT and MRI imaging

did not reveal major organ malformation or vascular abnormalities. Isolation and western blotting of several mouse brain regions showed that Leda-1/Pianp was expressed in all brain regions at variable levels. General and emotional behavioral tests showed that Leda-1/Pianp-/- mice were hyperactive under novel caging conditions and highly mobile under stressed conditions. These mice were also highly hesitant to explore novel objects, open arm of an elevated plus maze, brightly lit area and another social partner. These mice also showed impaired contextual learning, higher self grooming time and less nest building from cotton-nest. Overall these findings indicate functional involvement of Leda-1/Pianp in several brain functions including locomotor activity, stress coping, anxiety, learning and sociability.

Contact email address: siladitta05@gmail.com

Poster number: P-W018
Theme: Sensory & motor systems

Plasticity of visual cortex function in an adult mouse model of retinal ganglion cell loss

Authors: Asta Vasalauskaite, Frank Sengpiel - *School of Biosciences Cardiff University*, James E Morgan - *School of Optometry & Vision sciences Cardiff University*

Injury to optic nerve (ON) axons plays a major role in glaucoma progression. ON crush is an established model of axonal injury which results in retrograde degeneration and death of retinal ganglion cells (RGCs). However it is unknown how signal transmission to higher visual structures such as primary visual cortex (V1) is affected after ON crush.

Unilateral ON crush was performed on left eyes of adult C57BL/6 mice. Binocular V1 function of the contralateral (right) hemisphere was assessed longitudinally by optical imaging (OI) and in vivo two-photon calcium imaging under anaesthesia before and at 2d, 7d and 14d after ON crush. RGC numbers were quantified by counting Hoechst labelled cells in flat-mounted retinas.

We found a significant cell loss in the RGC layer compared to normal adults after 30 days ON crush. Cell loss occurred progressively with 15% of cells lost after 7 days and 43% of cells lost 14 days after ON crush. OI experiments demonstrated an immediate significant shift in ocular dominance index towards the ipsilateral, intact eye and an almost complete loss of response in V1 to contralateral eye stimulation in all ON crush animals. Additionally we found that response magnitude to ipsilateral eye stimulation significantly increased after long term ON crush. Two-photon experiments revealed that responses to ipsilateral eye stimulation were increased along with a significant increase in orientation selectivity index of neurons in layer 2/3 of binocular V1.

ON crush causes acute and permanent loss of signal transmission from the retina to V1. The observed increase of responsiveness in V1 to intact eye stimulation indicates that severe ON injury in adulthood may evoke cortical plasticity that is normally seen during the critical period.

Contact email address: Vasalauskaitea@cardiff.ac.uk

Poster number: P-W019
Theme: Sensory & motor systems

Mapping spatiotemporal calcium changes in mouse motor cortex during execution of a cued forelimb motor task

Authors: Brian Premchand, Julian Ammer, Joshua Dacre, Janelle Pakan, Nathalie Rochefort, Ian Duguid - *Centre for Integrative Physiology University of Edinburgh*

The primary motor cortex (M1) plays a fundamental role in the execution of skilled, dexterous motor behaviours. Descending motor output from cortical and brainstem motor areas shape the activity of spinal cord circuits to execute different types of movement from simple locomotion to skilled motor behaviours. Over the past century, work on human and non-human primates has significantly advanced our understanding of how cortical and brainstem motor areas coordinate their activity to achieve high-level motor control. But, how population representations of movement are organised in M1 still remains largely unresolved. To address this, we used two-photon calcium imaging of neuronal populations in head-restrained mice that were trained to execute a cued lever push-pull task for reward. Mice were injected with an adeno-associated virus (AAV1.Syn.GCaMP6s.WPRE.SV40) to express the genetically encoded calcium sensor GCaMP6s in layer 2/3 (L2/3) and layer 5 (L5) neurons in M1, habituated to head restraint and then trained to execute alternating lever push-pull actions in response to a 6kHz auditory tone (average training time to achieve

'expert' level: 11±2 days, 1 session/day). We performed population calcium imaging in contralateral forelimb M1 at depths corresponding to L2/3 and L5B, extracted ΔF/F values for individual neurons, and aligned them to behaviourally relevant time points (e.g. cue onset, movement onset, etc.). In a subpopulation of L2/3 and L5B neurons we observed tone-evoked calcium responses in trials where mice failed to execute a lever push or pull ("missed tone trials"), suggesting sensory-evoked responses likely contribute to M1 population responses during task engagement. During lever push-pull sequences, 96% of L2/3 neurons and 90% of L5B neurons displayed task-related activity with significant calcium changes seen during both push and pull movements. However, approximately 40% of L2/3 and L5B neurons displayed asymmetric calcium responses during push vs pull sequences, consistent with neuron-specific direction sensitivity in M1. Currently we are investigating the mechanistic underpinnings of direction sensitivity in M1 and how complex spatiotemporal patterns of L2/3 and L5B neuronal activity map onto different aspects of skilled forelimb behaviour.

Contact email address: s1347277@sms.ed.ac.uk

Poster number: P-W020
Theme: Sensory & motor systems

Orthogonalising parameters of predictive coding within a visuomotor adaptation task

Authors: Clare E Palmer - *Sobell Department of Motor Neuroscience and Movement Disorders UCL Institute of Neurology*, Dr Sasha Ondobaka - *WTCN UCL,* Dr James Kilner - *Sobell Department of Motor Neuroscience and Movement Disorders UCL Institute of Neurology*

Perturbations introduced in visuomotor adaptation tasks produce prediction errors, which are used to update forward models to generate more accurate sensorimotor predictions. Prediction errors are precision-weighted meaning an estimate of the inverse variance of the afferent signal (sensory precision) and the motor prediction (prior precision) is used to determine how readily prediction errors update forward models. These parameters are modulated during adaptation however their neurophysiological correlates are not fully understood. It has been suggested that beta oscillatory activity over sensorimotor cortex encodes this Bayesian updating process (Tan et al, 2014, 2016; Torrecillos et al, 2015). Here we designed a paradigm in which prediction errors were modulated orthogonally to precision parameters to determine their specific neurophysiological correlates. EEG was recorded from 24 subjects whilst they completed a visuomotor adaptation task in which angular perturbations were introduced into the visual feedback of a cursor during a finger reaching task on a track pad. High and low visual noise was introduced into the position of the cursor to modulate precision-weighting in a blockwise manner. A Bayesian hierarchical generative model (the HGF; Matthys et al, 2014) was used to track subjects' beliefs about motor predictions, prediction errors and precision estimates throughout the task and these were correlated with the EEG data.

A GLM including prediction error, prediction, sensory precision and prior precision was used to regress oscillatory activity in an ROI over sensorimotor cortex with each predictor. Analyses were carried out before a trial (aligned to the GO signal to move) to measure the role of preparatory beta activity, and after a trial (aligned to movement offset) to measure the role of the PMBS. The results showed that in both periods beta oscillatory activity significantly correlated with prior precision ($p<0.05$). The results suggest that sensorimotor beta activity encodes the uncertainty around updated Bayesian motor predictions necessary to adapt subsequent behaviour. Further analyses are required to compare different perceptual models and explore other neurophysiological correlates of these parameters outside of sensorimotor cortex.

Contact email address: clare.palmer.13@ucl.ac.uk

Poster number: P-W021
Theme: Sensory & motor systems

Lost in Space: graviceptive biasing of visual perception

Authors: Elisa Raffaella Ferre - *Psychology Royal Holloway University of London*, Timo Frett - *Institute of Aerospace Medicine Deutsches Zentrum für Luft- und Raumfahrt e.V. (DLR),* Javier Acedo - *Consulting Division Starlab Barcelona SL*, Patrick Haggard - *Institute of Cognitive Neuroscience University College London*

Our brain receives a series of sensory *snapshots* of the external world, which it must integrate to provide a description of the scenes around us. Vestibular inputs monitor changes in the position of the body relative to the environment. Here we tested the hypothesis that the vestibular system contributes to bridging the gap between successive visual snapshots of the external world. Accordingly, if gravitational signals provided by the vestibular organs cannot be aligned with those from vision, altered perceptual

experiences may occur. This might underlie perceptual errors reported by pilots and astronauts exposed to altered gravitational forces.

We investigated the contribution of vestibular-gravitational signals to the process of updating perception of a series of visual scenes. Ten participants were seated facing outwards on a short arm human centrifuge (SAHC) platform, which simulated 1 +Gz artificial gravity for ten minutes at head level. A visual judgement task was performed at normal gravity baseline and during 1 +Gz artificial gravity, in counterbalanced order. An environmental scene (Scene A) was followed after a short delay by a second scene (B) involving slight perspectival modification of Scene A. The scenes differed either in angular perspective (as if the participant had turned leftwards or rightwards during the delay) or in translational perspective (as if the participant had moved forward or backwards). Participants judged whether the implied viewpoint change between the first and second scene corresponded to a left/right-ward rotation (angular perspective), or to an approach/retreat (translational perspective).
Artificial gravity influenced the perceived relation between the visual images: participants judged the second scene as significantly closer during 1 +Gz artificial gravity compared to a normal gravity baseline ($t(9)=2.568$, $p=0.030$). No differences were found in judgements of angular perspective. This dissociation rules out non-specific effects of artificial gravity or centrifugation which cannot readily explain this specificity. Our results support a vestibular-driven updating process in which gravity signals are computed to provide a dynamic description of the spatial position of the body relative to the external environment.

Contact email address: E.Ferre@rhul.ac.uk

Poster number: P-W022
Theme: Sensory & motor systems

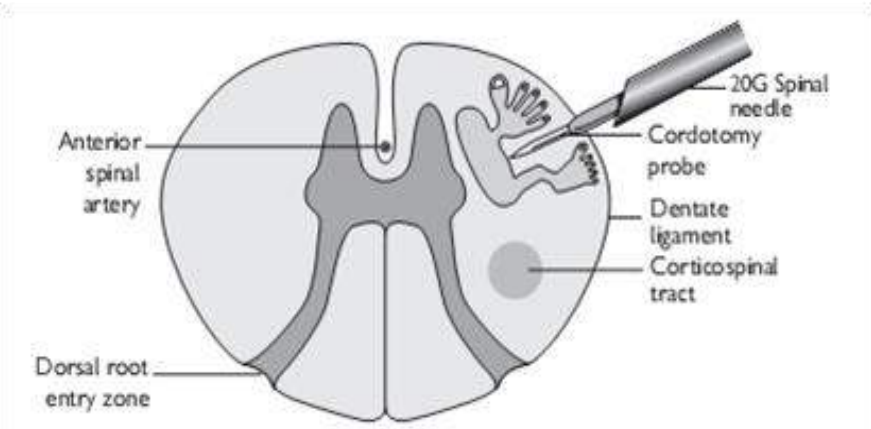
Alterations in itch, pain and pleasant touch following spinothalamic tract lesioning in humans

Authors: Francis McGlone - *Natural Sciences & Psychology Liverpool John Moores University*, Kate Marley - *Walton Centre for Neurology and Neurosurgery Aintree University Hospitals NHS Foundation Trust*, Andrew Marshall - *Natural Sciences & Psychology Liverpool John Moores University*

The spinothalamic tract (STT) forms the primary ascending projection system for thermoceptive and nociceptive A-delta and C-fibre afferents. On neuroanatomical grounds input from low threshold mechanosensitive C-Tactile (CT) afferents, which are hypothesised to encode the pleasant/affective nature of touch, and pruriceptors are also likely to ascend via the STT. However, direct evidence is lacking.

We assessed for alterations in affective touch and cowhage induced itch in patients undergoing STT lesioning for unilateral cancer related pain. STT lesioning resulted in contralateral thermal sensation deficits. Contralateral cowhage induced itch and pain was abolished. Pleasantness ratings for CT optimal (3cm/s) and sub-optimal (0.3 and 30cm/s) stroking touch showed no significant difference before and after lesioning or between lesioned and non-lesioned sides. However a significant contralateral reduction in CT preference index ([rating for 3cm/s x 2 - ratings for 0.3cm/s + 30cm/s] / 2) ($p<0.005$) was observed following lesioning. Ipsilateral itch and pleasant touch were unaffected.

The findings support the hypothesis that information salient to affective touch and pruriception ascend in the STT. Unlike the dramatic changes in thermoception, nociception and itch the effects on affective touch are subtle. This may reflect incomplete STT ablation or integration of A-beta and CT afferent inputs.



Contact email address: f.p.mcglone@ljmu.ac.uk

Poster number: P-W023
Theme: Sensory & motor systems

Neuropathic pain severity varies with spinal cord lesion level in neuromyelitis optica, a chronic neuroinflammatory condition

Authors: George Tackley - *Nuffield Department of Clinical Neurosciences Oxford University Hospitals NHS Trust, University of Oxford, Oxford, UK,* Domizia Vecchio - *Department of Neurology University of Piemonte Orientale, Novara, Italy*, Shahd Hamid - *Department of Neurology Walton Centre for Neurology and Neurosurgery, Liverpool, UK*, Maciej Jurynczyk, Yazhuo Kong, Rosie Gore - *Nuffield Department of Clinical Neurosciences Oxford University Hospitals NHS Trust, University of Oxford, Oxford, UK*, Kerry Mutch - *Department of Neurology Walton Centre for Neurology and Neurosurgery, Liverpool, UK*, Mark Woodhall, Patrick Waters, Angela Vincent, Maria Isabel Leite, Irene Tracey - *Nuffield Department of Clinical Neurosciences Oxford University Hospitals NHS Trust, University of Oxford, Oxford, UK*, Anu Jacob - *Department of Neurology Walton Centre for Neurology and Neurosurgery, Liverpool, UK*,J acqueline Palace - *Nuffield Department of Clinical Neurosciences Oxford University Hospitals NHS Trust, University of Oxford, Oxford, UK*

Rationale. Chronic neuropathic pain is a common, intractable and frequently debilitating consequence of neuromyelitis optica spectrum disorder (NMOSD) and has received relatively little attention in the literature, despite a prevalence within NMOSD of 80% and high subjective pain ratings(1). NMOSD is an immune mediated disorder that frequently targets the spinal cord causing inflammation, secondary demyelination and subsequent axonal loss and grey matter damage. This study investigates whether chronic pain severity in NMOSD relates to the craniocaudal location of culprit spinal cord lesions.

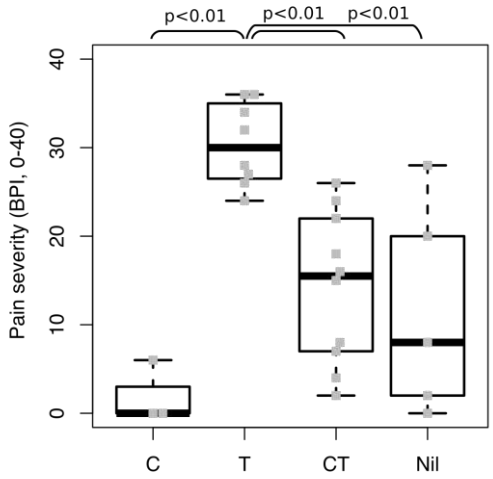
Method. Initially a retrospective cohort of 76 NMOSD patients from Oxford and Liverpool's national clinics were assessed for current pain (brief pain inventory, BPI) and craniocaudal location of cord lesion contemporary to pain onset (clinical MRI). A subsequent focused prospective MRI study of 26 NMOSD Oxford patients, a subset of the retrospective cohort, assessed current craniocaudal lesion location and current pain (again BPI).

Results. Patients with isolated thoracic cord myelitis at the time of pain onset were significantly more disabled and suffered more pain. Furthermore, cervical and thoracic lesions that persisted from pain onset to "out of relapse" prospective MRI had highly significant ($p<0.01$) opposing effects on pain scores (std.?= -0.46 and 0.48, respectively; see figure). Lesion length, total lesion burden and number of cord relapses did not correlate with pain.

Conclusions. Persistent, caudally located (i.e. thoracic) cord lesions in NMOSD patients associated with high chronic pain scores, irrespective of number of spinal cord attacks, lesion length, and lesion number. Although disability correlated with pain in isolation, it became an insignificant predictor of pain when regressed alongside craniocaudal location. A similar association of severe pain with thoracic cord lesions has been described in a related neuroinflammatory disorder and an autonomic hypothesis has been proposed(2).

1. Bradl, M. et al. Pain in neuromyelitis optica--prevalence, pathogenesis and therapy. Nat. Rev. Neurol. 10,529–536(2014)
2. Okuda, D. T. et al. Central neuropathic pain in MS is due to distinct thoracic spinal cord lesions. Ann. Clin. Transl. Neurol. 1,554-561(2014)

Figure. Pain severity vs. persistent cord lesion locations



BPI, brief pain inventory's pain severity index; C, isolated cervical cord lesions; T, isolated thoracic cord lesions; CT, cervicothoracic cord lesions; Nil, no visible lesions.
Boxplot figure calculated using first and third quartile, and median.

Contact email address: tackley@gmail.com

Poster number: P-W024
Theme: Sensory & motor systems

Sustained processing of sensory information during auditory perceptual decisions

Authors: Jiaxiang Zhang - *School of Psychology Cardiff University*, James Rowe - *School of Clinical Medicine University of Cambridge*
During perceptual decisions, converging findings from electrophysiological and neuroimaging studies suggest that, a decision variable integrates sensory information until reaching a decision threshold. This allows, as supported by recent evidence, rapid decisions to be committed long before the end of incoming sensory information. However, it is largely unknown whether the brain processes sensory information consistently during decision-making.

Here, we investigated the neural representations of sensory information throughout trials, combining electrophysiological recordings with high temporal resolution (magneto encephalography, MEG; and electroencephalography, EEG) and multivariate pattern recognition approaches. Neural dynamics were recorded using a 306-channel MEG system with concurrent 70-electrode EEG. Eighteen healthy participants were presented auditory click trains at 40 Hz. On each trial, the auditory stimulus was comprised of a 750 ms click train during which each click was binaural (uninformative segment), followed by a 1000 ms train during which each click was monaural (informative segment, i.e., each click presented to either to the left or the right ear). Participants were instructed to decide, at the end of each trial, whether the left or right ear received more clicks.

By parametrically changing the ratio of monaural clicks to left/right ears, decision accuracy varied from the chance level (50%) to 90%. On pre-processed MEG/EEG data, we used linear support vector machine with cross-validation procedure to classify from all sensors and electrodes, at each time point, trials presented with left vs. right clicks. Classification accuracy on transit information from click trains was significant ($p<0.05$, FDR corrected) throughout the informative segment, at around when the stimulus was delivered, with a peak delayed by 150~200 ms. Classification accuracy at the uninformative segment remained at the chance level.

Our findings suggest that electrophysiological responses are constantly sensitive to incoming sensory information, regardless whether a pending decision has been made. Therefore, the human brain may process sensory evidence independent of cognitive demands, with relevant information being encoded in the cortex.

Contact email address: zhangj73@cardiff.ac.uk

Poster number: P-W025
Theme: Sensory & motor systems

Manipulating endocannabinoid signalling in an awake animal model of tinnitus

Authors: Joel Berger, Ben Coomber, Samantha Hill, Adam Hockley, William Owen - *Institute of Hearing Research Medical Research Council*, Steve Alexander - *Faculty of Medicine & Health Sciences University of Nottingham*, Alan Palmer, Mark Wallace - *Institute of Hearing Research Medical Research Council*

Animal models of tinnitus have revealed long-term hyperexcitability and altered neural synchrony, thought to arise from pathology affecting the balance between excitation and inhibition in the auditory system. This balance is regulated by neuromodulators, such as endogenous cannabinoids (endocannabinoids). Cannabinoid drugs are potent anti-nociceptive agents in models of chronic neuropathic pain, a condition that shares substantial parallels with tinnitus, i.e. phantom sensory percept in the absence of sensory input, initiated peripherally through deafferentation and subsequently involving central mechanisms. We therefore sought to determine whether the highly-selective CB_1 agonist arachidonyl-2'-chloroethylamide (ACEA) could abolish putative neural mechanisms of tinnitus.

Guinea pigs (GPs) were first implanted with electrocorticography (ECoG) multi-electrode assemblies. Following baseline data collection, GPs were given intraperitoneal injections of either (1) sodium salicylate in order to induce tinnitus (350 mg kg^{-1}; $n = 8$), (2) salicylate co-administered with ACEA (1 mg kg^{-1}; $n = 5$), or (3) ACEA alone (1 mg kg^{-1}; $n = 4$). Resting-state and auditory-evoked neural activity recorded in awake GPs was compared between groups. Hearing status was assessed using the auditory brainstem response (ABR).

Cluster-based permutation analysis indicated that salicylate altered resting-state activity, specifically by reducing alpha band activity (6-10 Hz) in cortical oscillations. Auditory-evoked responses were also enhanced (between 79-145%), whilst wave I ABR amplitudes

were significantly decreased at 20 kHz ($p < 0.01$ for both left and right ears). Co-administration of ACEA still resulted in slight reductions in ABR amplitudes, but these were no longer significant ($p = 0.07$ left ear; $p = 0.2$ right ear). Decreases in oscillatory activity at 6-10 Hz were no longer evident, although enhanced cortical potentials were still present (between 61-159%). Administration of ACEA alone did not significantly affect auditory system function.
These data indicate that manipulating endocannabinoid signalling in a tinnitus model can affect some of the underlying neural mechanisms. We are currently collecting data to determine whether ACEA can also abolish behavioural evidence of tinnitus.

Contact email address: joel.berger@nottingham.ac.uk

Poster number: P-W026
Theme: Sensory & motor systems

Thalamocortical control of skilled motor behaviour

Authors: Joshua Dacre, Julia Schiemann, Alex Harston, Ian Duguid - *Centre for Integrative Physiology and Patrick Wild Centre, Edinburgh Medical School: Biomedical Sciences, University of Edinburgh, Scotland, UK, EH8 9XD. University of Edinburgh*

The primary motor cortex (M1) is a key brain area for the generation and control of complex motor movements. Output from M1 can be driven by long-range inputs from a collection of thalamic nuclei termed the motor thalamus (MTh). However, the role of MTh and precisely how its activity shapes the membrane potential dynamics of M1 projection neurons during skilled motor behaviour remains largely unresolved. To address this issue we first defined the 3D anatomical coordinates of mouse forelimb motor thalamus (MThFL) by employing conventional retrograde and viral-based tracing methods targeted to mouse forelimb motor cortex (M1FL). These complementary approaches defined MThFL as a ~0.8 mm wide cluster of neurons with central coordinates 1.1 mm caudal, 0.9 mm lateral to bregma and 3.2mm below the pial surface. Thus, MThFL incorporates defined areas of the ventrolateral, ventral anterior and anteromedial thalamic nuclei. To investigate the role of M1FL and MThFL during skilled motor behaviour, we developed and optimised a quantitative behavioural paradigm in which head-restrained mice execute a cued lever push task for reward. Forelimb movement trajectories were mapped using high-speed digital imaging and multi-point kinematic analysis. Independently inactivating M1FL or MThFL using a pharmacological strategy resulted in altered forelimb kinematic trajectories and a significant reduction in task performance in skilled mice. By combining whole-cell patch-clamp electrophysiology and two-photon population imaging in M1FL, single unit recordings in MThFL, and optogenetic manipulation strategies in vivo, we have generated new insights into how motor thalamus shapes motor cortical output and skilled motor behaviour.

Contact email address: joshua.dacre@ed.ac.uk

Poster number: P-W027
Theme: Sensory & motor systems

Different components of beta oscillations related to movement preparation and movement execution revealed by beta frequency rTMS

Authors: Liora Michlin - *Nuffield Department of Clinical Neurosciences University of Oxford*, Juan Francisco Martín Rodríguez - *Laboratorio de Trastornos del Movimiento Instituto de Biomedicina de Sevilla*, Huiling Tan, Peter Brown - *Nuffield Department of Clinical Neurosciences University of Oxford*

Voluntary movement is accompanied by changes in beta oscillations in the motor cortex. This study uses rhythmic TMS (rTMS) at the individual's motor beta frequency to modulate beta oscillations during the movement preparation phase, allowing us to explore their causal role in encoding the uncertainty of future movements and features of the movement execution itself.
18 participants performed a delayed reaching task. During the movement preparation phase, directional uncertainty about the upcoming movement was manipulated by varying the number of spatial cues (1, 3 or 12 spatial cues indicated potential locations for the target). Afterwards, another cue was presented indicating the actual target, upon which participants were instructed to move a joystick-controlled cursor to the target in a ballistic movement as quickly and accurately as possible. Participants performed 4 blocks in counterbalanced order (72 trials each): 1 without stimulation, and 3 'stimulation condition'. In the latter, 10 TMS pulses were delivered over the contralateral motor hand area during the movement preparation phase of each trial. The trains of pulses were either regular at individual beta frequency, or irregular with random intervals as a control. EEG was continuously acquired from 23 sites, while measuring the reaction time, movement velocity, and accuracy of each movement.

We found that increased target uncertainty resulted in increased reaction time (p<.001) and less beta desynchronization during movement preparation (bilaterally, p=.007). However, target uncertainty did not change the level of beta following presentation of the definitive target (p=.347), and did not affect the maximal speed (p=.511) or accuracy of movement execution (p=.055). Beta frequency rTMS did not change the reaction time or its dependence on uncertainty; rather, it led to a decrease in maximal speed of the forthcoming movement (p<.001) independent of the uncertainty condition, compared to irregular rTMS.
These results suggest there may be two broad components to beta oscillations in motor cortex: the first is spread bilaterally over the motor cortex, related to overall motor readiness, and modulated by uncertainty. The second is more lateralised and related to the actual execution of the movement.

Contact email address: liora.michlin@new.ox.ac.uk

Poster number: P-W028
Theme: Sensory & motor systems

Action-focused approach to perceptual decision making

Authors: Maciej Szul - *CUBRIC Cardiff University*, Petroc Sumner - *School of Psychology Cardiff University*, Jiaxiang Zhang - *CUBRIC Cardiff University*

Simple button presses are the most common response modality used in cognitive testing. However, it is an oversimplification of continuous and dynamic decision-action cycles in our daily lives. Here, in two perceptual decision-making experiments, we first investigated the validity of using joystick as a way of collecting responses (experiment 1), then demonstrated the contextual effect of preceding actions on forthcoming decisions in continuous action paradigm (experiment 2).

In experiment 1, participants were instructed to detect the coherent motion direction of random dot kinematogram from four possible alternative directions. In two counterbalanced sessions, responses were collected either using button presses or joystick movements. Bayesian multivariate test showed strong evidence in favour of the hypothesis, that the decision-making is not affected by response modality (reaction time: logBF=2.25; response accuracy: logBF=10.05). Furthermore, responding using joystick enabled to extract measures, describing action components unobservable in key presses (e.g., latency of movement's peak velocity, and precision of direction detection).

In experiment 2, participants were instructed to perform continuous circular movements using joystick (clockwise/anti-clockwise), in response to the coherent motion direction in random dot kinematogram. In the second half of each trial, there was 50% probability that motion coherence and motion direction would change, signalling the change of circular movement direction. Bayesian multivariate test showed strong evidence for latency of action change being affected by motion strength (logBF=12.78). Lowered motion strength affected the accuracy more than change of direction only. Moreover, in trials when both direction and motion strength changed, accuracy was the lowest (logBF=15.46). Therefore, contextual information affected the subsequent decision processes.

Our findings suggested that joystick is a viable way to acquire behavioural responses in rapid decisions, with response profiles comparable to traditional button presses. Detailed view of the action, with relation to the sensory input, can help investigate sensory and motor components of sensorimotor transformation.

Contact email address: SzulMJ@cardiff.ac.uk

Poster number: P-W029
Theme: Sensory & motor systems

A dynamic neural circuit model of decision confidence, change of mind, and multimodal actions

Authors: Nadim Atiya - *Neural Systems and Neurotechnology, Intelligent Systems Research Centre, School of Computing and Intelligent Systems University of Ulster,* Arkady Zgonnikov - *School of Psychology, and Complex Systems Research Centre National University of Ireland, Galway*, Petri T. Piiroinen - *School of Mathematics, Statistics and Applied Mathematics, and Complex Systems Research Centre National University of Ireland, Galway*, Denis O'Hora - *School of Psychology, and Complex Systems Research Centre National University of Ireland, Galway*, KongFatt Wong-Lin - *Neural Systems and Neurotechnology, Intelligent Systems Research Centre, School of Computing and Intelligent Systems University of Ulster*

Several psychological and neurophysiological studies have suggested that decision-making is linked to the accumulation of evidence over time. Decision-making is often accompanied with decision confidence, in which lower decision confidence more likely leads to change of mind. There is also significant neural evidence that the brain uses error monitoring mechanisms to monitor and correct potential errors. These phenomena provide evidence of metacognition in animals and humans. While current computational models especially those based on post-decisional evidence accumulation provide good quantitative fit to behavioural data, they are abstract and do not provide neurally plausible assumptions nor take into account error-correction mechanisms.

This work proposes a computational neural circuit model of perceptual decision-making that can account for decision confidence, change of mind, and multimodal action outputs. The model, building on previous biological models of perceptual decision-making, consists of a decision module, a metacognitive module, and motor output modules. The modules are modelled by nonlinear firing-rate type neural model that exhibit winner-take-all behaviour. Our model is then applied to account for data from a perceptual decision-making experiment that we have previously conducted. The experiment has explored the relationships among saccadic eye movement, hand movement, and choice behaviour in a well-known motion discrimination task ("random dots") paradigm. Our model can account for the psychophysical data and eye-hand trajectories, including change of mind trials. Finally, our model has dynamic features that can allow it to potentially adapt to other task paradigms.

Overall, we have developed a neural circuit model that sheds light on the interactions among decision confidence, metacognition and multimodal actions.

Contact email address: Atiya-N@email.ulster.ac.uk

Poster number: P-W030
Theme: Sensory & motor systems

Planum Temporale in People who Stutter

Authors: Patricia Gough - *Psychology Maynooth University*, Emily Connally - *Experimental Psychology & FMRIB centre University of Oxford*, Peter Howell - *Psychology University College London*, David Ward - *School of Psychology and Clinical Language Sciences University of Reading*, Jennifer Chesters, Kate Watkins - *Experimental Psychology & FMRIB centre University of Oxford*

Previous studies have reported that the planum temporale - a language-related structure that normally shows a leftward asymmetry – had reduced asymmetry in people who stutter (PWS) and reversed asymmetry in those with severe stuttering. These findings are consistent with the theory that altered language lateralization may be a cause or consequence of stuttering. Here, we re-examined these findings in a larger sample of PWS. We evaluated planum temporale asymmetry in structural MRI scans obtained from 67 PWS and 63 age-matched controls using: 1) manual measurements of the surface area; 2) voxel-based morphometry to automatically calculate grey matter density. We examined the influences of gender, age and stuttering severity on planum temporale asymmetry.

Results showed that the size of the planum temporale and its asymmetry were not different in PWS compared with Controls using either the manual or the automated method. Both groups showed a significant leftwards asymmetry on average (about one-third of PWS and Controls showed rightward asymmetry). Importantly, and contrary to previous reports, the degree of asymmetry was not related to stuttering severity. In the manual measurements, women who stutter had a tendency towards rightwards asymmetry but men who stutter showed the same degree of leftwards asymmetry as male Controls. In the automated measurements, Controls showed a significant increase in leftwards asymmetry with age but this relationship was not observed in PWS.

We conclude that reduced planum temporale asymmetry is not a prominent feature of the brain in PWS and that the asymmetry is unrelated to stuttering severity.

Contact email address: patricia.gough@nuim.ie

Poster number: P-W031
Theme: Sensory & motor systems

The effect of observing a magnified and minified mirror reflection of the hand on contact thermal heat pain in healthy participants

Authors: Priscilla Wittkopf, Tarek Jafar, Paul Sharples, Mark Johnson - *School of Clinical and Applied Sciences Leeds Beckett University*

Background
Mirror visual feedback is used to treat painful conditions associated with alterations of body image resulting from neuropathy, amputation and complex regional pain syndrome. In clinical practice, mirror feedback techniques tend to use normal-sized reflections of body parts. The findings of studies on pain patients and healthy participants exposed to noxious stimuli suggest that observing magnified and minified body parts using mirrors, lenses, or virtual reality may affect pain perception. However, the direction of effect varies between studies. The aim of this study using healthy participants was to compare the effect of observing a magnified and minified reflection of the hand in front of a mirror on the intensity of experimentally-induced contact heat pain of the hand hidden behind the mirror.

Methods
A within-subject repeated-measures design was used with three reflection conditions (normal sized, magnified and minified) and two view contexts (reflected hand and box where participants observed a reflection of their left hand covered by a cardboard box). Participants rated the intensity (NRS) of noxious heat stimuli set at a temperature 2°C above pain threshold and delivered to the skin of the right hand using a 30x30 mm thermode attached to a TSA-II Neurosensory.

Results
Eighteen pain-free healthy volunteers (10 females; mean ± SD age = 24.3 ± 3.1 years) participated in the study. There was a significant main effect of reflection ($F(2,34) = 6.48$, $p = 0.004$, $\eta_p^2 = 0.276$, power = 0.88). Pairwise comparisons showed that pain intensity was less when looking at the minified reflection compared with the magnified reflection (mean ± SD = 3.96 ± 1.75, 4.88 ± 1.31, respectively; $p=0.001$) but there were no differences between normal-sized reflection and magnified nor minified reflection ($p > 0.05$). There was no significant main effect of view context or reflection x view context interaction (all $F's < 4.86$, n.s.).

Conclusion
Participants reported less pain when looking at a minified reflection irrespective of the reflection being of the hand or box. We are unable to determine at this stage whether this is a true finding or a result of methodological shortcomings contributing to a false negative finding.

Figure 1. Experimental set up. Participants were seated and the right hand was placed on the contact-thermode behind the mirror and the left hand on a sham thermode in front of the mirror.

Contact email address: p.wittkopf@leedsbeckett.ac.uk

Poster number: P-W032
Theme: Sensory & motor systems

Anisotropy of human motor cortex responses to non-invasive stimulation: implications for the study of brain-behaviour relationships

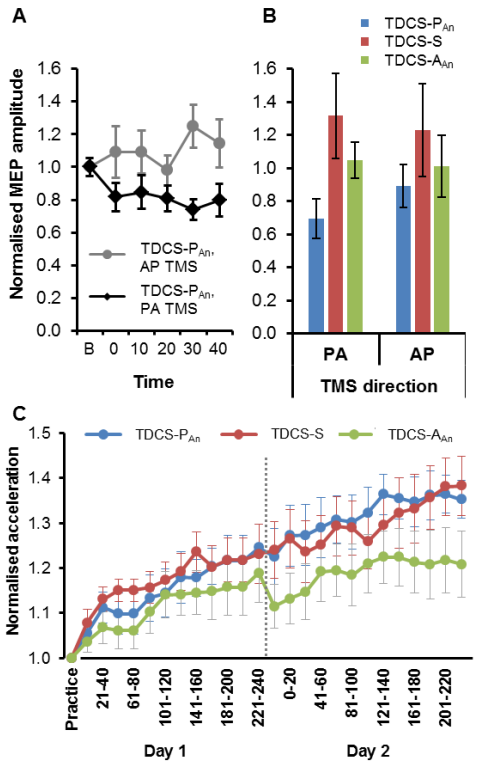
Authors: Ricci Hannah, Anna Iacovou, Vishal Rawji, John C Rothwell - *Sobell Department of Motor Neuroscience and Movement Disorders UCL Institute of Neurology*

Introduction
It is well known that different directions of transcranial magnetic stimulation (TMS) current activate the motor cortex in different ways. A posterior-anterior (PA) induced current recruits a different sets of inputs onto the corticospinal neurones than the opposite anterior-posterior (AP) current. We recently found that pre-conditioning these two sets of inputs with TMS produced distinct effects on different types of motor learning [Hamada et al (2014), J Neurosci, 34, 12837]. We hypothesised that these circuits would differ in their sensitivity to the orientation of transcranial direct current stimulation (TDCS) currents, and that this would in turn influence the effects of concurrent TDCS and motor practice on physiological and behavioural outcomes.

Methods
Human volunteers received TDCS via two electrodes placed 3cm in front and 3cm behind the motor hotspot for the hand with either an anterior anode (A_{An}), posterior anode (P_{An}) or sham (S) TDCS. The electrodes were aligned with the preferred orientation of PA TMS. Expt.1: 15 volunteers received TDCS-P_{An} for 10min at 1mA. MEPs evoked by PA and AP TMS pulses were measured before and at 10min intervals afterwards. Expt. 2: 30 volunteers received TDCS-P_{An}, TDCS-A_{An} or TDCS–S during practice of a ballistic thumb acceleration task, which was used to assess motor learning and retention (48h). PA- and AP-evoked MEPs were recorded before and after practice on day 1.

Results
Expt. 1: TDCS with a posterior anode 21uppressed PA evoked MEPs to 75% of control values, but had no significant effect on AP evoked MEPs. Expt. 2: PA-evoked MEPs were suppressed after motor practice with TDCS-P_{An} compared to with TDCS-A_{An} and TDCS-S. TDCS-A_{An} tended to impair 48h consolidation of motor learning and overall learning on day 2 compared to TDCS-P_{An} and TDCS-S.

Discussion
The primary motor cortex is highly sensitive to the direction of TDCS current flow. This is relevant physiologically in terms of effects on MEPs and appears to also be behaviourally relevant in terms effects on motor learning and retention. Given the similar organization across the neocortex, we expect that the anisotropy of stimulation applies to other areas of cortex, such as those more involved in cognition.



TDCS with anode posterior to motor hotspot (P_{an}) suppressed PA-evoked MEPs (PA TMS) and had no effect on AP-evoked MEPs (AP TMS) **(A).** PA MEPs were suppressed after TDCS-P_{An} and motor practice on day 1 compared to the other conditions **(B)**. Retention of motor learning at 48h (start of day 2) tended to be impaired by TDCS-A_{An} compared with TDCS-P_{An} and TDCS-S **(C)**.

Contact email address: r.hannah@ucl.ac.uk

Poster number: P-W033
Theme: Sensory & motor systems

Neuronal Origin of the Negative BOLD response: a TMS-EEG-MRS Investigation

Authors: Ross Wilson - *Psychology (BUIC) University of Birmingham*, Dr Craig J. McAllister - *School of Sport, Exercise and Rehabilitation Sciences University of Birmingham,* Dr Martin Wilson - *BUIC University of Birmingham*, Dr Stephen D. Mayhew - *Psychology (BUIC) University of Birmingham (BUIC)*

Background
Unilateral sensorimotor stimulation induce negative BOLD fMRI responses (NBR: decrease from baseline) in ipsilateral sensorimotor cortex (S1/M1). Cross-modal NBRs can also be evoked in unstimulated sensory cortex.
Animal data suggest NBRs may represent GABAergic inhibition via decreased neuronal activity. In humans, functional significance of NBR and its relation to cortical excitability is unclear.
Here we used MRI and concurrent TMS-EEG during sensory tasks to link changes in motor-evoked potential (MEP) measures of cortical excitability to neural activity and individual NBR and GABA levels.

Methods
In 17 young-adult subjects four tasks were used to evoke S1/M1 NBR: right median nerve stimulation (MNS); sustained right-hand pinch-grip; visual full-field 7Hz reversing checkerboard; auditory beeps at 7Hz.
We measured subjects NBR (8/16s on/off) to each task and right M1 GABA concentration with 3T MRI.
In a second session we measured changes in EEG alpha and beta power to each stimulus (9/12s on/off), whilst single-pulse TMS to right M1 induced MEPs in the left thumb at: 1s (sT1), 7s (sT2), 11-12s (rebound, RB) and 18s (baseline, BL) post task onset. MEP differences between timings were examined by ANOVA.

Results
Significant MEP differences were found during: MNS, BL-sT1 ($p=0.034$) and BL-RB ($p=0.023$); motor, BL-sT2 ($p=0.027$). No visual/auditory MEP differences were found (Fig1 C).

We observed bilateral S1/M1 de-synchronisation of EEG alpha and beta power during MNS and motor, strongest in left S1/M1 (Fig1 B). Visual or auditory stimuli evoked little S1/M1 response.
NBRs were observed in right S1/M1, in order of magnitude: MNS, motor, auditory, visual (Fig1 A). GABA significantly correlated with MNS and motor NBR, with no correlations found for visual/auditory.
Conclusion
MNS results suggest corticospinal excitability decreases are coincident with NBR in that region. While motor NBR was coincident with significant sT2 MEP increase .
The lack of a MEP-NBR correlation during visual/auditory stimuli suggests a different origin of cross-modal NBR, reflected in GABA/NBR correlations.
Further work to correlate: subject's MEP changes to NBR; EEG response in S1/M1 to MEP changes and NBR.

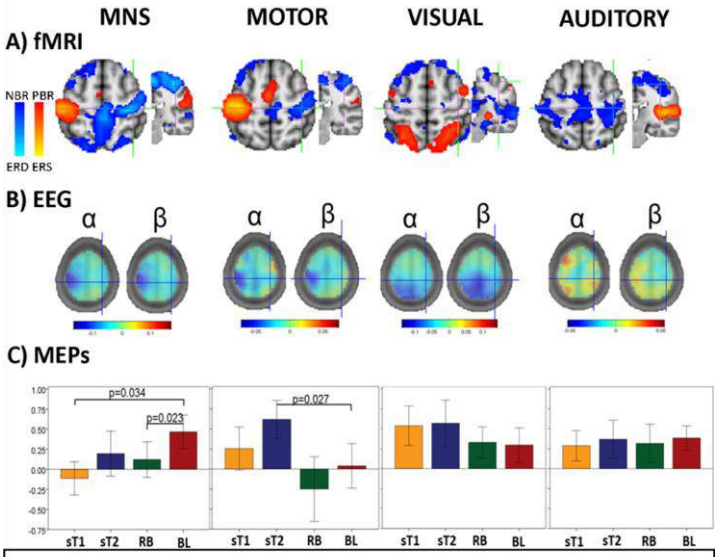


Fig. A) Group average main effect BOLD responses to MNS, motor, visual and auditory st/imuli; red=PBR, blue=NBR. B) Group average EEG alpha and beta beamformer map to each stimulus. C) mean amplitude MEP change from baseline for each timepoint during each stimulus.

Contact email address: rxw494@student.bham.ac.uk
Poster number: P-W034
Theme: Sensory & motor systems

Evaluation of factors influencing the relationship between physical activity, the perception of pain and psychological attitudes to pain in humans.

Authors: Samantha Waite, Stuart Egginton - *School of Biomedical Sciences University of Leeds*, Donna M Lloyd - *School of Psychology University of Leeds*, Anne E King - *School of Biomedical Sciences University of Leeds*

A complex relationship exists between physical activity levels, psychological attitudes to pain and pain perception. In this study, quantitative sensory testing (QST) was utilized before and after acute exercise to determine whether this can modify an individual's pain thresholds. In another study, psychological profiling was undertaken in subjects reporting variable levels of exercise engagement in their normal routine to assess a putative link between physical activity and attitudes to pain.

Thermal pain perception pre- or post-exercise was assessed using a QST protocol (Pathway System, MEDOC, Israel) for measurement of hot (HPT) or cold pain CPT) thresholds. Aerobic exercise was with a cycle ergometer (70-75% max heart rate) and isometric exercise used a hand-grip dynamometer (25% of maximum voluntary contraction, 5 repeats). For psychological traits, Fear of Pain (FoP) and Pain Catastrophizing (PC) questionnaires were used with subjects declaring their routine cardio activity levels as never/once per month (p/m); 1-3 times per week (p/w) or >3 times p/w. All protocols had local ethical approval.

After isometric exercise, the CPT was significantly lower (20.4oC in control versus 17.4oC with exercise, $P<0.05$, n=7) – indicative of ongoing hypoalgesia. A hypoalgesic trend was also observed for HPT i.e. a post-exercise increase in HPT although data were not significant ($P>0.05$). After aerobic exercise, the CPT was significantly lower, indicating induction of hypoalgesia (15.3oC in control versus 4.61oC with exercise, $P<0.05$, n=6) whereas the HPT was unaltered. With respect to exercise engagement, participants engaged in exercise >3 times p/w showed significantly lower PC scores compared to those with less engagement, for example once p/m (>3 times p/w, mean score = 3.3; once p/m = 17.4; $P<0.05$, n=39). Similarly for FoP scores, the lowest values were observed in those exercising >3 times p/w.

Overall, these preliminary data support the view that bursts of acute physical activity can modify an individual's pain experience, as measured by QST. Furthermore, high levels of physical activity engagement are linked to psychological traits such as low PC and FoP but further studies are needed to establish the existence of a causal link.

Contact email address: samanthajwaite1@gmail.com

Poster number: P-W035
Theme: Sensory & motor systems

Learned sensorimotor representations in mouse auditory cortex revealed with two-photon calcium imaging

Authors: Samuel A M Picard, Yves Weissenberger, Andrew J King, Johannes C Dahmen - *Department of Physiology, Anatomy & Genetics University of Oxford*

Predicting the sensory consequences of one's actions is critical to perception and action in dynamically changing environments. In many cases, there is a fixed, general relationship between a given action and its sensory consequences, such as visual flow during locomotion. Oftentimes, however, the sensory consequences of an action are highly context specific and must remain plastic. To cope with this, humans and animals are thought to build and store internal models (Wolpert et al., 1998), traditionally associated with cerebellum-like structures. More recently however, neurons have been reported in primary visual cortices, which signal mismatch between predicted and actual sensory feedback (Keller et al., 2012). It currently remains unclear whether cortical mismatch signals are specific to fixed sensorimotor contingencies or whether they may also arise with arbitrary, newly learned contingencies.

We developed and validated a novel task that requires head-fixed mice to learn novel, arbitrary motor-auditory associations. Animals were trained to freely "navigate" through a one-dimensional, abstract auditory landscape of equally spaced pure tones, by licking either of two lick-ports (see Figure). We show that mice are capable of using auditory feedback to adaptively guide behaviour, and are sensitive to unexpected feedback. Next, we used two-photon calcium imaging to investigate the functional properties of auditory cortical neurons in mice performing this task. Among the various acoustic tuning profiles encountered in auditory cortex, some otherwise sparsely active neurons were found to be particularly responsive following sounds that violated the learned sensorimotor contingency (see Figure). This activity was dependent on whether or not the animal was actively engaged in the task. Taken together, these results suggest that a network of neurons in auditory cortex is engaged in predicting the sensory consequences of motor actions, even when the relation between motor action and sensory feedback is arbitrary and newly learned.

Acknowledgements
Supported by the Wellcome Trust

References
Keller GB, Bonhoeffer T, Hübener M (2012), Neuron 74:809–815.
Wolpert DM, Miall RC, Kawato M (1998), Trends Cogn Sci 2:338-347.

Contact email address: samuel.picard@dpag.ox.ac.uk

Poster number: P-W036
Theme: Sensory & motor systems

Diminished Interference of Motor Memories in People with Parkinson's Disease

Authors: Sarah Voets - *School of Sport, Exercise and Rehabilitation Sciences University of Birmingham*, John-Stuart Brittain - *Nuffield Department of Clinical Neurosciences University of Oxford*, Chris Miall - *School of Psychology University of Birmingham*, Ned Jenkinson - *School of Sport, Exercise and Rehabilitation Sciences University of Birmingham*

Previous studies have suggested that people with Parkinson's disease (PD) are not as efficient as age-matched controls in retaining certain kind of motor memories. We sought to investigate this phenomenon more thoroughly by testing for interference effects using force-field adaptation. Motor learning can be tested in the laboratory using motor tasks that perturb sensorimotor feedback (e.g. prism adaptation). Often, after learning such an adaptation a motor memory of the perturbation is formed, so that when exposed to the same perturbation for a second time performance is improved (also called savings). Motor memories can also contribute to an interference effect. This effect occurs when memory of a learned adaptation makes it harder to learn an opposite

adaptation. We hypothesized that if motor memory is less robust in people with PD they should display smaller savings and diminished interference. Fourty-eight people with PD (PwPD) and 48 healthy age-matched controls performed a force-field adaptation paradigm with their upper-limb to test motor learning and motor memory. Participants held the handle of a robotic arm and made repetitive movements from a central location to a single-target. Initially all participants learned to adapt to a clockwise force-field (12 N/m/s) that was imposed on the handle during reaching. Recall (i.e. savings) of the learned force-field was tested after a 1-hour or 24-hour break, or – to measure the amount of interference - performance on adapting to an opposite (counter clockwise) force-field was tested instead. Therefore, both PwPD and Controls were split up into 4 subgroups, each of n=12. Results reveal that PwPD (1hour subgroup) show similar improvement compared to Controls (1h) when tested for savings, but display less interference when tested on the opposite force-field. These results are comparable to the 24-hour subgroups and were reflected both in the lateral deflection and force production. In line with our hypothesis we observed a reduction of interference in PwPD compared to Controls. In contrast, the amount of savings was similar for both groups. These results suggest that motor memory may still be preserved in PD and that the altered interference might be caused by problems with motor memory retrieval.

Contact email address: S.H.E.M.Voets@pgr.bham.ac.uk

Poster number: P-W037
Theme: Sensory & motor systems

Gene Expression Changes in the Mouse Spiral Ganglion Following Noise Induced Hearing Loss

Authors: Sherylanne Newton - *Neuroscience, Psychology and Behaviour University of Leicester,* Mike Mulheran - *Medicine & Social Care Education University of Leicester*, Blair D. Grubb - *Faculty of Health and Life Sciences University of Liverpool*, Ian D. Forsythe - *Neuroscience, Psychology and Behaviour University of Leicester*

Noise induced hearing loss (NIHL) is classically divided into permanent or temporary forms. Individuals with temporary threshold shifts (TTS) will experience elevated hearing thresholds immediately following noise exposure, which resolves over several days or weeks. TTS was once thought to cause little lasting damage to the hair cell stereocilia or supporting structures in this form of auditory insult. However, recent evidence suggests TTS triggers “silent damage”: a type of neuropathic damage where there are reduced numbers of hair cells synapses onto spiral ganglion neuron (SGN) processes and secondly where a slowly developing neuronal death exacerbates presbyacusis (Kujawa & Liberman, J. Neurosci, 26: 2115-23. 2006; Jensen, et al., PLoS One 10. 2015). Previous studies of gene expression changes following noise insult have used whole cochlea preparations that do not differentiate between the changes in the different cochlear structures. Here we have used micro-dissection of the modiolus to focus on the SGNs and minimise the contribution from other cochlea structures.

CBA/Ca, female, P40 mice were exposed to 105 dB SPL (sound pressure level) broadband noise for 1.5hrs under anaesthesia. Age matched controls (sham) were also anaesthetised for 1.5 hours and exposed to silence. Auditory brainstem recordings (ABRs) were taken before noise exposure and at the time of tissue collection, showed the exposure protocol produced an immediate threshold shift of 36±3 dB SPL (Click) which recovers to 10±3 dB SPL by 28d. Mice were divided into three groups, and allowed to recover for 24hrs, 7d or 28d following exposure. After recovery, the modiolus was micro-dissected from both cochleae. RNA-Sequencing was performed on the Illumina NexSeq500 at the Deep Seq facility at the University of Nottingham.

Preliminary analysis of the RNA-Sequencing data has revealed 421 differentially expressed genes over this 28 day time period. In addition to changes in 57 neuron specific genes, Gene Ontology analysis shows that the acute phase inflammatory response persists over the 28d period, with chronic upregulation of apolipoproteins (A1, C1 & H), serum amyloids (A1/A2), serum albumin, and complement C3.

Contact email address: sn207@le.ac.uk

Poster number: P-W038
Theme: Sensory & motor systems

Neuronal activity in the dorsal striatum during sleep in mice: homeostatic regulation and relationship to cortical firing

Authors: Tomoko Yamagata, Laura E McKillop, Nanyi Cui - *Department of Physiology, Anatomy and Genetics University of Oxford,* Anri Sato - *Department of Applied Information Sciences, , Graduate School of Information Sciences Tohoku University*, Simon P Fisher, Vladyslav V Vyazovskiy - *Department of Physiology, Anatomy and Genetics University of Oxford*

Cortical network activity during NREM sleep is dominated by slow waves, which are associated with reduced neuronal firing and are enhanced after sleep deprivation (SD). Although the network slow oscillation was originally described in the striatum, the effects of SD on the neuronal activity in this region has received little attention. In this study, we recorded local field potentials (LFPs) and neuronal spiking activity from the dorsal striatum (n=7) and the motor cortex (n=4) during NREM sleep in freely moving C57BL/6J mice. Mice were recorded during an undisturbed baseline day and after 6 h SD.

In both the cortex and striatum, the LFPs during NREM sleep were dominated by slow waves in the frequency range 0.5-4Hz (slow wave activity, SWA). As expected, positive peaks of LFP slow waves recorded in the cortex were associated with reduced neuronal activity. Slow waves recorded in the striatum were not merely volume conducted, but correlated with locally recorded neuronal spiking. However, in contrast to the cortex, positive LFP slow waves recorded in the striatum were associated with an increase in spiking, which was preceded and followed by a pronounced suppression of activity.

NREM sleep after SD was characterised by higher LFP SWA in both the striatum (first 2h: mean±SEM 178.2±8.9% change relative to baseline day) and the frontal cortex (mean±SEM first 2h: 166.9±6.2%), and was not significantly different between the two regions. Notably, in both regions, the surge of MUA after the period of reduced firing, occurred on average approximately 40 m earlier during recovery sleep after SD as compared to baseline.

This is the first report that sleep slow waves in the striatum are homeostatically regulated in mice. Our data suggest that increased sleep pressure affects both local neuronal activity in the striatum as well as the large-scale network activity within the corticostriatal circuit.

Acknowledgement:
BBSRC (BB/K011847/1), MRC (MR/L003635/1), FP7-PEOPLE-CIG (PCIG11-GA-2012-322050), Wellcome Trust (098461/Z/12/Z), The Uehara Memorial Foundation (TY), The Naito Foundation (TY).

Contact email address: tomoko.yamagata@dpag.ox.ac.uk

Poster number: P-W039
Theme: Sensory & motor systems

Dissecting direct and indirect pathways between ventral premotor cortex and the spinal cord by transcranial magnetic stimulation

Authors: Karen Bunday - *Sobell Department of Motor Neuroscience and Movement Disorders University College London*

Anatomical studies in non-human primates have shown that the ventral premotor cortex (PMv) has a number of indirect projections to the cervical spinal cord [e.g. via the primary motor cortex (M1) and the brainstem], but also provides direct projections terminating predominantly in the upper and less in lower cervical segments. Since PMv plays such a critical role in the control of hand movements it is somewhat paradoxical that direct projections to lower cervical segments are sparse. In humans, it is classically thought that PMv contributes to hand movements via dense corticocortical connections with M1, yet whether there are direct projections to the spinal cord remains unknown. Here we used transcranial magnetic stimulation (TMS) over PMv to condition H-reflexes elicited via peripheral nerve stimulation (PNS) whilst subjects sat at rest. TMS was delivered over the caudal part of the inferior frontal gyrus, while PNS was applied to the median nerve in order to elicit H-reflexes in the flexor carpi radialis muscle. Descending and ascending volleys arriving onto the spinal motoneurons were timed accurately by measuring the central conduction time (measured from M1) and peripheral nerve stimulation time for each volunteer. H-reflexes were either elicited alone (baseline) or conditioned by PMv TMS. We investigated 6 inter-stimulus intervals (ISI), namely -4, -2, 0, 2, 4 and 6 ms, and 3 TMS intensities (80%, 100% and 120% of resting motor threshold). Our results show that while threshold conditioning pulses over PMv had no effect on H-reflexes, subthreshold and suprathreshold PMv conditioning pulses significantly facilitated H-reflexes at a later ISIs (4 ms; 2 and 6 ms, respectively). Additional experiments revealed that these effects were not due to a spread of activation from PMv to M1 and that longer central conduction times could involve the propriospinal network. Our results allow us to speculate that recruiting sub- or suprathreshold PMv projections reveals a different time course of possible slower direct or indirect interactions. PMv projections have a net and diffused facilitatory effect on spinal excitability; with subthreshold and suprathreshold outputs interacting directly or indirectly with lower cervical segments.

Contact email address: k.bunday@ucl.ac.uk

Poster number: P-W040
Theme: Neuronal, glial & cellular mechanisms

Examining obesity-induced sensitivity to neuroinflammation

Authors: Anne-Marie Howe, Kelly M. McNamara, Conor P. Duffy, Fiona C. McGillicuddy - *UCD School of Medicine University College Dublin*, Neil G. Docherty, Carel W. le Roux - *UCD School of Medicine University College Dublin*, Derek A. Costello - *UCD School of Biomolecular & Biomedical Science University College Dublin*

Obesity is a low-grade inflammatory condition, associated with an increased risk of age-related cognitive decline, dementia and Alzheimer's disease (AD). The factors predisposing the obese population to cognitive impairment remain poorly understood, but are believed to include insulin resistance, ER stress and neuroinflammation. AD is characterised by the deposition of the toxic peptide amyloid-β (Aβ) in the brain; the primary inflammatory stimulus. The role of toll-like receptors (TLRs) in mediating Aβ-induced inflammatory changes has been widely reported and we, among others, have highlighted the involvement of TLR2 in promoting Aβ-induced microglial activation and neuronal dysfunction. In addition, we have described the contribution of infiltrating peripheral macrophages to facilitating the neuroinflammatory environment and neuronal impairment associated with ageing.

While not all obese people will develop AD, subsets of the obese population are clearly more vulnerable. We hypothesise that obesity promotes the sensitivity of macrophages to inflammatory challenge, which access the brain and likely amplify Aβ-induced neuroinflammation. Here we have assessed TLR2- and TLR4-mediated inflammatory responses in bone marrow-derived macrophages (BMDMs) prepared from genetically obese animals, and from an animal model of diet-induced obesity (DIO). In addition, we have examined the impact of macrophage-derived inflammatory mediators on the activation of microglia.

The difficulty maintaining weight-loss in the obese population has recently received significant attention. This highlights the importance of developing strategies to alleviate the risk of co-morbidities, despite weight-loss. We have extended our analysis to examine whether weight-loss is essential to alleviate obesity-related inflammatory sensitivity. We have compared the responsiveness of BMDMs from obese rats following gastric bypass surgery, and a mouse model of DIO consisting of a diet rich in monounsaturated fats to promote metabolic health, despite obesity. We report that surgical-induced weight-loss consistently alleviates obesity-related sensitivity to TLR stimulation. However, a metabolically healthy obesogenic diet can also attenuate specific obesity-induced changes.

Contact email address: anne.howe@ucdconnect.ie

Poster number: P-W041
Theme: Neuronal, glial & cellular mechanisms

Down regulation of G proteins affects tolerance to alcohol in Drosophila melanogaster

Authors: Benjamin Aleyakpo - *School of Health Sport and Bioscience University of East London*

Ethanol consumption induces both acute and chronic behavioural changes. At the molecular level, ethanol interacts with GABA and Glutamate receptors and induces the release of both endorphins and dopamine in the brain. We have previously shown that chronic alcohol intake affects differential expression of specific G proteins in Drosophila melanogaster brain when measured by RT-PCR. We have since developed flies that express siRNA for Gi and Gq in a temperature sensitive manner and demonstrate that G protein down-regulation alters the normal alcohol tolerance behaviour. Flies exposed to ethanol for three consecutive days typically display an increase in the sedation time (measured as ST50: time at which half of a group of flies is sedated). The mutant flies carrying the siRNA genes showed normal tolerance behaviour when maintained at 18°C but activating siRNA expression at 30°C significantly increased their sedation time at day one with no further increase in additional exposures. This further demonstrates that G protein expression plays a key role in the alcohol induced sedation behaviour which is leading us to investigate whether the G proteins coupled to GABA-B receptors contribute to tolerance.

Contact email address: b.aleyakpo@uel.ac.uk

Poster number: P-W042
Theme: Neuronal, glial & cellular mechanisms

Non-parametric directionality analysis of intra-hippocampal interactions during kainic acid induced epileptiform activity in a rat model of epilepsy.

Authors: David Halliday - *Electronics University of York,Mohd Harizal Senik - School of Life Sciences University of Nottingham*, Carl W. Stevenson - *School of Biosciences University of Nottingham*, Rob Mason - *School of Life Sciences University of Nottingham*

The ability to infer directionality between neural signals is an important aspect of quantifying neuronal interactions, typically using parametric approaches based on auto regressive models for the neural signals. Here we explore the use of a non-parametric approach, where directionality is decomposed into forward, reverse and zero-lag components. The study assesses directionality in left and right hippocampal CA1 and CA3 and local field potential (LFP) recordings before and after local unilateral kainic acid (KA)-induced epileptiform activity in a rat model of mesial temporal lobe epilepsy (mTLE). Isoflurane-anaesthetised Lister-hooded rats (300-400g; n=6) had microelectrode arrays positioned in the left and right hippocampus. A cannula was attached for local injection of kainic acid (KA) in the left hippocampus (HPC). After 30 min basal recording, KA (1 mM, 1 µL) was administered into the left HPC. LFP activity was recorded using a Plexon MAP system. All procedures were carried out in accordance with the Animals (Scientific Procedures) Act 1986, UK. The non-parametric directionality analysis was undertaken by splitting each 3.5 hr recording into 1 minute non overlapping segments and performing directionality analysis on each segment. The directionality analysis decomposes the coherence into three components, here we consider the forward and reverse components. KA injection interrupted the directionality between LFP signals. In the ipsilateral (left) HPC it led to a decrease in the forward component from CA3 to CA1, resulting in an increased CA1 to CA3 coherence. In the contralateral (right) HPC the effect was less clear, but there was a tendency to promote an increased CA3 to CA1 coherence. Bilateral interactions in the basal period were predominantly from left HPC to right HPC, these were reduced in magnitude following KA injection. The results demonstrate that non-parametric directionality analysis can detect externally induced changes in LFP interactions and can quantify the changes in coherence that result.

Contact email address: david.halliday@york.ac.uk

Poster number: P-W043
Theme: Neuronal, glial & cellular mechanisms

The role of LGI1 in epilepsy

Authors: Eleonora Lugarà, Elodie Chabrol, Matthew Walker - *Department of Clinical and Experimental Epilepsy UCL*

The neuronal extracellular matrix has a pivotal role in physiology and in pathophysiological conditions such as epilepsy. LGI1 (Leucine Rich Glioma Inactivated 1) is a secreted trans-synaptic protein which interacts presynaptically with Kv1.1 potassium channels and ADAM23. Postsynaptically, LGI1 influences AMPA and NMDA receptors through a direct link with the ADAM22 adhesion protein. Mutations of LGI1 lead to a familiar form of temporal lobe epilepsy with audiogenic features. However, the role of LGI1 in acquired epilepsy and how acute reduction of interactions between LGI1 and its pre- and post-synaptic partners affects temporal lobe circuits and synaptic transmission in epilepsy remains unclear.

Currently, we are testing a knock down approach to reduce LGI1 expression in vitro using shRNA delivery by viral vectors. First, we recorded neuronal network activity using a MEA (microelectrode array) system. We observed a two-fold increase in the MFR (mean firing rate) of the cultures transfected with shRNA compared to controls. We also used a complementary approach monitoring seizure-like activity in vitro with calcium imaging in high density cultures exposed to picrotoxin. Treatment with LV-shRNA-LGI1 increased the frequency of calcium bursts.

Parallel in vivo experiments on rats aim to understand if LGI1 concentrations in the brain are affected after generation of spontaneous seizures. In particular, we used the perforant path stimulation model of chronic temporal lobe epilepsy. Induction of limbic status epilepticus with stimulation of perforant path fibres, results in later spontaneous seizures in the hippocampus and long-lasting tonic clonic attacks which begin a few days after the treatment. Results show a sharp decrease of LGI1 concentrations three weeks after severe status epilepticus within the ipsilateral side of the hippocampus.

Taken together our results show that LGI1 concentrations directly influence spontaneous network activity and seizure-like activity in vitro and that LGI1 expression in the hippocampus is altered after 21 days of chronic epilepsy in freely behaving rats.

Contact email address: e.lugara@ucl.ac.uk

Poster number: P-W044
Theme: Neuronal, glial & cellular mechanisms

Effect of phencyclidine pretreatment on amphetamine and nicotine evoked brain activation, measured by pharmacological magnetic resonance imaging

Authors: Ersin Yavas - *Neuroscience, Psychology & Behaviour University of Leicester*, Justyna Janus, Michael Kelly - *Core Biotechnology Services University of Leicester*, Andrew Young - *Neuroscience, Psychology & Behaviour University of Leicester*

The non competitive NMDA receptor antagonist, phencyclidine (PCP) causes behavioural deficits in experimental animals, which model schizophrenia, reflecting glutamate hypoactivity in the disease. Dopamine (DA) signalling is also disrupted in schizophrenia raising the possibility of a dysregulation of glutamate/DA signalling in expression of symptoms. In addition, acetylcholine, which is known to modulate DA release in striatum, also shows changes after PCP pretreatment: thus altered DA function after PCP may be mediated through disruption of cholinergic signalling, either indirectly via glutamatergic control of cholinergic activity, or through a direct effect of PCP on cholinergic receptors. However, the extent to which PCP activation of the cholinergic system leads to psychotomimetic effects is not yet clear. We hypothesis that PCP treatment affects DAergic transmission through either direct or indirect effects on cholinergic systems.

We have investigated the effect of subchronic pretreatment with PCP or saline on dopaminergic and cholinergic activation of the brain measured by pharmacological magnetic resonance imaging (phMRI). Animals were scanned twice at weekly intervals, under isoflurane anaesthetic, using a 9.4T preclinical MRI scanner (Agilent Technologies), and the effects of amphetamine and nicotine injections on blood oxygenation dependent (BOLD) contrast were assessed. They were then treated with PCP (2mg/kg, twice daily for 5 days) and left drug free for 10 days, before repeating the drug challenges during phMRI.

Both amphetamine and nicotine increased BOLD signal in cortical and striatal areas of the brain. Preliminary first-level analysis of phMRI data shows enhancement of amphetamine-stimulated BOLD signal, and attenuation of nicotine-stimulated BOLD activation following PCP treatment. These experiments show the utility repeated phMRI in rats to measure changes in transmitter systems following PCP pretreatment, modelling schizophrenia, and that PCP pretreatment causes opposite changes in responsiveness to amphetamine and nicotine. Therefore, cholinergic systems may be important in the dysregulation of dopaminergic transmission seen after PCP pretreatment, and may be important for understanding dysfunctions underlying schizophrenia.

Contact email address: ey28@le.ac.uk

Poster number: P-W045
Theme: Neuronal, glial & cellular mechanisms

Phase-amplitude coupled persistent theta and gamma oscillations in rat primary motor cortex in vitro.

Authors: Gavin Woodhall, Nicholas W Johnson, Stuart Greenhill, Ian Stanford - *Life and Health Sciences Aston University*

In vivo, theta (4-7 Hz) and gamma (30-80 Hz) neuronal network oscillations are known to coexist and display phase-amplitude coupling (PAC). However, in vitro, these oscillations have for many years been studied in isolation. Using an improved brain slice preparation technique, we have, using co-application of carbachol (10 µM) and kainic acid (150 nM), elicited simultaneous theta (6.6 ± 0.1 Hz) and gamma (36.6 ± 0.4 Hz) oscillations in rodent primary motor cortex (M1). Each oscillation showed greatest power in layer V. Using a variety of time series analyses (Modulation Index, wavelet ridge analysis, bi-coherence and bi-spectral analyses) we detected significant cross-frequency coupling in some, but not all, preparations.

Differences were observed in the pharmacological profile of each oscillation. Thus, gamma oscillations were reduced by the GABAA receptor antagonists, gabazine (250 nM and 2 µM), and picrotoxin (50 µM) and augmented by AMPA receptor antagonism with SYM2206 (20 µM). In contrast, theta oscillatory power was increased by gabazine, picrotoxin and SYM2206. GABAB receptor blockade with CGP55845 (5 µM) increased both theta and gamma power, and similar effects were seen with diazepam, zolpidem, MK801 and a series of metabotropic glutamate receptor antagonists. Oscillatory activity at both frequencies was reduced by the gap junction blocker carbenoxolone (200 µM) and by atropine (5 µM). These data show theta and gamma oscillations in layer V of rat M1 in vitro are cross-frequency coupled, and are mechanistically distinct, being generated by both synaptic and non-synaptic mechanisms.

Contact email address: g.l.woodhall@aston.ac.uk

Poster number: P-W046
Theme: Neuronal, glial & cellular mechanisms

Neddylation-dependent degradation of DNMT3A1 promotes activity-dependent bdnf promoter demethylation, synaptic plasticity and spatial memory

Authors: Gonca Bayraktar, Michael R. Kreutz - *Neuroplasticity Leibniz Institute for Neurobiology*

One key epigenetic writer is *de novo* DNA methyltransferase DNMT3A1 however not much is known on its regulation at protein level in the context of neuronal plasticity contributing to learning and memory. In our study we showed that nuclear protein levels of DNMT3A1 are tightly controlled by the activation of synaptic GluN2A subunit-containing NMDA receptors. Signalling from NMDARs led to the proteasomal degradation of DNMT3A1. We revealed a novel neddylation-dependent molecular mechanism executing the degradation of DNMT3A1. Our findings showed that this mechanism operates via the neddylation of the E3-ubiquitin ligase Cullin-4B in an activity dependent manner and this in turn ubiquitylated DNMT3A1. Further we found that nuclear DNMT3A1 protein levels in CA1 neurons are reduced following the induction of NMDAR-dependent LTP and also in an intact *in vivo* system following object location learning in mice. Neddylation-dependent degradation of DNMT3A1 resulted in hypomethylation of the *Bdnf* promoter IV, increased *Bdnf* IV expression, and promoted late long-term potentiation (LTP). Occluding the NEDD8 pathway interrupted activity-dependent de-methylation of the *Bdnf* promoter, late LTP and novel object location memory.

Contact email address: gonca.bayraktar@lin-magdeburg.de

Poster number: P-W047
Theme: Neuronal, glial & cellular mechanisms

Modulation of RNA editing in cell lines endogenously expressing AMPA receptor subunits through the use of antisense oligonucleotides.

Authors: Ilda Sethw Hassan, Philip E. Chen - *School of Biological Sciences Royal Holloway, University of London*

RNA editing is a posttranscriptional modification mechanism that changes gene-specified codons. One of the main forms of RNA editing is the conversion of adenosine to inosine by the enzyme adenosine deaminase (ADAR) acting on the RNA of the GluA2 subunit of AMPA receptors. AMPA receptors (AMPARs) are a subset of ionotropic glutamate receptor composed of one or more of four subunits (GluA1-4). AMPARs play a central role in normal and abnormal synaptic function within the nervous system and incorporation of the GluA2 subunit is required to reduce calcium permeability. RNA editing is essential for reducing calcium permeability in AMPARs. Deficient RNA editing has been shown to trigger significant neuron cell death and evidence for this has been found in patients with motor neuron disease. Phosphorodiamidate morpholino oligonucleotides (PMOs) have previously been shown to manipulate RNA editing in HeLa cells, but we have little information on how PMOs can be utilised to manipulate RNA editing in cell lines that endogenously express the GluA2 subunit.

In this study, we sought to investigate the effects of specifically targeted PMOs that manipulate the alternative splicing of ADAR2 in SH-SY5Y cells. ADAR2 exists as multiple splice variants and some of these exhibit decreased RNA editing efficiency.
The effects of the PMOs on RNA editing were assessed by transfecting them into SH-SY5Y cells over 24-48 hour incubation periods. Editing levels were measured following RT-PCR of RNA extracted from transfected cells and densitometric analysis of a *BbvI* restriction digestion. Preliminary experiments have shown that the PMOs were able to induce alternative splicing events in SH-SY5Y cells, where a 20% increase in exon skipping of the AluJ cassette was observed. Furthermore, an increase in RNA editing levels by 10% was observed compared to baseline levels.

This data shows that the PMOs are able to manipulate RNA editing in cell lines endogenously expressing GluA2. This suggests that there is potential for use as a motor neuron disease treatment. However further research is currently underway to investigate other potential effects and to elucidate cellular mechanisms regulating RNA editing in AMPA receptors.

Contact email address: Ilda.SethwHassan.2015@live.rhul.ac.uk

Poster number: P-W048
Theme: Neuronal, glial & cellular mechanisms

Sex differences on sequential activation of Microglia and Astrocyte following postnatal systemic immune challenge

Authors: Inssaf Berkiks, Aboubaker Elhessni - *Biology Laboratory of Genetic, Neuroendocrinology and Biotechnology, Faculty of Sciences, Ibn Tofail University, Kenitra. Morocco*

Early immune challenges induce long-lasting brain developmental and behavioral impairments and increase the risk of diseases later in adulthood (Stoll, Hansen et al. 2004). The activation of the immune system results in the release of proinflammatory cytokines, such as interleukin-1β (IL-1β), tumor necrosis factor α (TNF-α) and IL-6 (Aderem and Ulevitch 2000). High levels of these cytokines during development are associated with low resilience to diseases in adulthood (Shi, Fatemi et al. 2003, Boisse, Mouihate et al. 2004, Yu, Yuan et al. 2004). The recent study demonstrated that the glial cells has a sequential activation, for example, the height level of cytokines production during the inflammation activate the microglia fist which leads to activate the astroglia after (Norden, Trojanowski, Villanueva, Navarro, & Godbout, 2015).

To compare the behavioral responses of the glial cells after LPS peripheral administration in PND14 in (2, 4, 24 and 48h) time points in both of sexes. By measuring the cytokines, and oxidative stress level. Our preliminary results showed that the NO level increased significantly in hippocampus and prefrontal cortex male after 2h from the LPS injection, this level returned to the normal level after 24h, while the female NO levels increased significantly after 4h from the LPS administration and continued to increase until 48h from the LPS injection. These results suggest subtle differences between males and females in the neonatal response to LPS administration.

Contact email address: berkiksinssaf@gmail.com

Poster number: P-W049
Theme: Neuronal, glial & cellular mechanisms

Endocytic route of ApoER2 receptor in presence of its ligand Reelin

Authors: Jessica Santana, María Paz Marzolo - *Cellular and Molecular Biology Pontifical Catholic University of Chile*

Reelin is an extracellular glycoprotein essential for the development of laminated cortical brain structures in vertebrates. Disruption on Reelin receptor ApoER2 results in cognitive dysfunction in rodents and detectable layering defects in the cortex and hippocampus. Although, the downstream signaling of ApoER2 has been widely described, little is known about its traffic in presence of ligand. Our laboratory has previously demonstrated that ApoER2 is internalized through a Clathrin-Dependent Endocytosis (CDE) under basal conditions and dependent on the NPxY cytoplasmic motif of the receptor and that the receptor has a long half life. Besides CDE there are Clathrin-Independent (CIE) pathways, including one regulated by the small GTPase Arf6 which regulates membrane trafficking and actin cytoskeleton at the plasma membrane. It is known that expression of an active form of Arf6 leads to generation of a vacuolar structures where cargos stay herein, blocking the convergence with early endosomes. Here, in HeLa cells co-expressing ApoER2 receptor and Arf6WT, we show for the first time that ApoER2 reached Arf6 positive endosomes 5 minutes after internalization and stays herein even after 40 minutes. More interesting, ApoER2 with its ligand Reelin reached Arf6WT compartments already at 5 minutes and then experience a drastic decline at 20 minutes suggesting that the presence of Reelin might alter the traffic of the receptor. We also follow ApoER2 arrival to Rab5 endosomal compartments in the absence and in the presence of reelin. Without ligand, around 30% of the internalized ApoER2 gets into Rab5 compartment at 5 minutes. In contrast, when the receptor bound reelin, only 5% were in Rab5 positive compartment at 5 minutes. Altogether, these results suggest that ApoER2 has at least two different routes of internalization. We also found that ApoER2 receptors life time is shorter in presence of Reelin and is more ubiquitinated. Additionaly, in the presence of Reelin, ApoER2 is able to arrive to a Rab7 positive endosome in cells with a block in CDE. Finally, here we have some approaches of this in hippocampal neurons supporting the hypothesis of the existence of CDE and CIE routes for ApoER2 endocytosis.

Support by Fondecyt Regular 1150444

Contact email address: jssantan@gmail.com

Poster number: P-W050
Theme: Neuronal, glial & cellular mechanisms

Silencing astrocytic glucocorticoid receptors alters synaptic activity of mouse nucleus accumbens neurons

Authors: : Joanna Ewa Sowa, Marcin Siwiec - *Department of Physiology Institute of Pharmacology, Polish Academy of Sciences, 31-343 Krakow, Smetna street 12, Poland*, Urszula Skupio, Magdalena Tertil, Ryszard Przewlocki - *Department of Molecular Neuropharmacology Institute of Pharmacology, Polish Academy of Sciences, 31-343 Krakow, Smetna street 12, Poland*, Krzysztof Tokarski, Grzegorz Hess - *Department of Physiology Institute of Pharmacology, Polish Academy of Sciences, 31-343 Krakow, Smetna street 12, Poland*

The activity of the nucleus accumbens (NAc) is crucial for the integration of rewarding, motivational and emotional processes. Therefore, alterations in NAc activity can play a vital role in the pathophysiology of depression, particularly through mediating motivational processes and anhedonia. Stress is involved in the pathophysiology of depressive disorders, due to, among others, alternations in glucocorticoid receptor (GRs)-dependent functions. Increasing evidence points to astrocytes as key mediators of GR-dependent effects in the brain. Even though astrocytes are well-equipped to integrate neuronal information through ion channels and neurotransmitter receptors, they have often been neglected in neurophysiology research.

The aim of this study was to evaluate the effect of silencing the astrocyte GR on membrane properties and basal excitatory synaptic transmission in NAc medium spiny neurons. We have injected lentiviral vectors with Cre activated shRNA cassete silencing GRs into ventral striatum of transgenic mice expressing Cre recombinase under the aldehyde dehydrogenase 1 family promoter (Aldh1L1Cre), specific for astrocytes. C57BL/6 mice injected with lentiviral vector were used as a control group. Whole-cell patch clamp recordings were performed using acute brain slices (300µm) containing the NAc. For each cell the resting membrane potential, input resistance, excitability and spontaneous postsynaptic excitatory currents (sEPSC) were determined.
Our results indicate that medium spiny neurons surrounded by GR-ablated astrocytes did not differ in intrinsic membrane properties such as membrane resistance, resting membrane potential and excitability. However, deletion of GRs in astrocytes attenuated sEPSC amplitude while increasing the intrinsic excitability of recorded neurons. This suggests a multifaceted effect of astrocyte GR ablation, involving postsynaptic changes and possibly homeostatic plasticity mechanisms affecting neural output.
In conclusion, our data show that selective silencing of GR in NAc astrocytes has a profound effect on NAc synaptic activity, indicating that the astrocytic response to glucocorticoids can be an active modulator of neuronal activity in the reward circuitry which may have important scientific and therapeutic implications.

Contact email address: joasowa@if-pan.krakow.pl

Poster number: P-W052
Theme: Neuronal, glial & cellular mechanisms

In search of a novel receptor for L-Lactate in the brain.

Authors: Kasumi Kishi - *School of Physiology, Pharmacology and Neuroscience University of Bristol*, Patrick S Hosford - *Centre for Cardiovascular and Metabolic Neuroscience, Neuroscience, Physiology and Pharmacology University College London*, Valentina Mosienko - *School of Physiology, Pharmacology and Neuroscience University of Bristol*, Giorgia Jurisic, Klaus Seuwen, Bernd Kinzel, Marie-Gabrielle Ludwig - *Developmental & Molecular Pathways Novartis Institutes for Biomedical Research*, Jack A Wells, Isabel N Christie, Alexander V Gourine - *Centre for Cardiovascular and Metabolic Neuroscience, Neuroscience, Physiology and Pharmacology University College London*, Anja G Teschemacher, Sergey Kasparov - *School of Physiology, Pharmacology and Neuroscience University of Bristol*

Our group has previously shown that L-Lactate released from astrocytes or applied locally activates neurones of the locus coeruleus (LC) and leads to release of noradrenaline. An involvement of the cAMP-PKA cascade was also demonstrated. It was hypothesised that the effect is mediated by a G-protein coupled receptor (GPCR). Among poorly characterised receptors revealed in the LC by transcriptomic analysis was GPR4, a proton-sensing GPCR. We therefore decided to investigate whether it could be involved in L-Lactate-mediated cAMP signalling. We found that L-Lactate appears to act as a negative allosteric modulator of GPR4, causing concentration and pH-dependent inhibition of cAMP accumulation. We also characterised the GPR4 antagonist NE 52-QQ57 developed by Novartis and found it to be a highly potent competitive antagonist of protons with an IC50 of 26.8nM. Based on the previously hypothesised roles of GPR4 in the brain, NE 52-QQ57 was then used in vivo in rats to investigate possible effects on hemodynamics, BOLD responses to sensory stimulation, and respiratory responses to hypercapnic stimulation. Our results suggest that the biological activity of GPR4 via the cAMP axis is very limited and probably not critical for the immediate, short term phenomena. Moreover, in vivo GPR4 is under the tonic inhibitory effect of L-lactate. We believe that cAMP-independent signalling

pathways or GPR4-mediated changes in gene expression may be more important in chronic situations such as new vessel formation and cancer where a role for GPR4 has been documented.

Contact email address: kasumi.kishi@bristol.ac.uk

Poster number: P-W053
Theme: Neuronal, glial & cellular mechanisms

BDNF promotes the formation of axonal morphology through Ras-GRF1-mediated R-Ras activation

Authors: Kentaro Umeda, Hironori Katoh, Manabu Negishi - *Graduate School of Pharmaceutical Sciences Kyoto University*

R-Ras, a Ras-family small GTPase, has crucial roles in the regulation of axonal morphology, including axon guidance, outgrowth and branching formation. A member of Ras-family small GTPases serves as molecular switch between GDP-bound inactive state and GTP-bound active state. Activation of them requires GDP-GTP exchange catalyzed reaction by guanine nucleotide exchange factors (GEFs) and only activated form is able to bind to its downstream effectors. We have revealed that R-Ras controls axonal morphology through many cytoskeletal regulators such as afadin, integrin and CRMP-2. However, the upstream signal for R-Ras activation is poorly understood. In this study, we are trying to identify the key players for R-Ras activation and elucidate their precise regulatory mechanisms.

Here we report that Brain-derived neurotrophic factor (BDNF) treatment resulted in the activation of endogenous R-Ras activity and the promotion of axonal branching formation in primary cultured cortical neurons. In addition, BDNF-induced promotion of axonal branching was not observed when the expression of R-Ras was down-regulated using RNAi technology. BDNF belongs to the neurotrophin family of growth factors and known to be important for neuronal survival, growth and differentiation. Recently, it has been reported that the level of BDNF secretion in brain is correlated to the onset of psychiatric disorders and therefore BDNF has been highlighted as effective therapeutic target.

We also investigated the molecular events that connect extracellular BDNF stimulation to intracellular R-Ras activation. We focused on Ras-GRF1, a member of GEFs for R-Ras. Ras-GRF1 was reported to bind to the intracellular region of TrkB, the receptor tyrosine kinase harboring high affinity for BDNF. We observed that BDNF treatment dramatically increased serine phosphorylation of Ras-GRF1, the important residue for its GEF activity. Moreover, the knockdown of Ras-GRF1 suppressed BDNF-induced promotion of axonal branching formation. These results suggest that BDNF promotes axonal branching formation via phosphorylation of Ras-GRF1 and following R-Ras activation. This work exhibits the potential involvement of BDNF in R-Ras-mediated axonal morphological regulation and its underlying cellular mechanisms.

Contact email address: umeda.kentaro.36u@st.kyoto-u.ac.jp

Poster number: P-W054
Theme: Neuronal, glial & cellular mechanisms

Increased excitability of presynaptic afferents contributes to DHPG-LTD of evoked synaptic responses in rat ventral hippocampal slices

Authors: Patrick Tidball, Stephen M Fitzjohn, Graham L Collingridge - *Physiology, Pharmacology & Neuroscience Univeristy of Bristol*

Activation of group I mGluRs (mGlu1 and mGlu5) by the agonist (RS)-DHPG is known to induce long-term depression of synaptic transmission (LTD) and to persistently modulate intrinsic neuronal excitability in rodent hippocampal slices. However, the precise mechanisms involved in DHPG-mediated plasticity remain elusive, and it is not clear if synaptic and intrinsic forms of plasticity induced by DHPG are entirely separate phenomena, or if they interact. In this study, we have used electrophysiological recordings to further characterise DHPG-LTD in the CA1 area of slices taken from the dorsal (DH) and ventral (VH) sectors of the adult rat hippocampus, and have considered whether changes in neuronal excitability might play a role in this form of synaptic plasticity.

In extracellular recordings, a brief DHPG application (100 µM, 10 min) resulted in a substantially larger magnitude of LTD in VH compared to DH slices. This enhanced DHPG-LTD in VH slices was associated with a larger increase in paired-pulse facilitation when compared to the LTD induced in DH slices. DHPG treatment also resulted in a small but sustained depression of the

pharmacologically isolated fibre volley in slices from the VH. In whole-cell patch clamp experiments from VH CA1 pyramidal neurons, DHPG treatment resulted not only in LTD of evoked synaptic responses, but also in a large and persistent increase in the frequency of spontaneous synaptic events. This effect was driven by the spontaneous discharge of presynaptic afferent fibres, since it was blocked by TTX, suggesting a role for enhanced excitability in the modulation of synaptic transmission by DHPG. We tested this hypothesis by applying the Kv7 channel opener and anticonvulsant retigabine to VH slices 30 min after DHPG treatment, and found that it partially reversed LTD. In contrast, retigabine applied to naïve slices caused a depression of responses.

Our results show that VH slices have a greater ability to exhibit DHPG-LTD than their DH counterparts. We propose that an enhancement of excitability by DHPG contributes to the larger LTD in VH slices by increasing the spontaneous firing rate of the presynaptic afferent fibres and subsequently increasing the number of refractory synapses present during a given evoked event.

Contact email address: p.tidball@bristol.ac.uk

Poster number: P-W055
Theme: Neuronal, glial & cellular mechanisms

Axonal microRNAs in the regulation of axon development and brain connectivity

Authors: Raquel Mesquita-Ribeiro - *School of Life Siences University of Nottingham*, Alex Rathbone - *University of Nottingham*, Nitzan Herzog, Noah Russell, Federico Dajas-Bailador - *Faculty of Engineering University of Nottingham*

Cognitive brain function requires the establishment of neuronal networks, which rely on the formation and elongation of axonal projections and the differentiation of presynaptic terminals during development. The cellular events involved in these processes are dependent on protein synthesis localized to the axon, which enables dynamic changes of the axonal proteome in response to neurotrophic cues that guide axons towards their postsynaptic partners with spatiotemporal precision.

MicroRNAs are short non-coding RNAs known to regulate protein expression by controlling mRNA translation repression/degradation. Recently, these regulatory RNAs have emerged as key players in the modulation of several molecular pathways underlying neuronal differentiation in early stages of development. However, their role in the axon, in particular axonal outgrowth and presynaptic differentiation, is only beginning to be unravelled.

Microfluidic culture models allow the functional compartmentalization and fluidic isolation of axons from their cell bodies (Fig1.a). Using next generation sequencing we identified a set of microRNAs enriched in the axonal fraction of primary cortical cultures, which were further validated by RT-qPCR. Candidate microRNAs were quantified over different developmental stages in cortical cultures (day in vitro 2, 5 and 12) to pinpoint highly expressed axonal microRNAs potentially involved in axon and neuron network development. Following the characterization of axonal microRNA expression levels, we selected miR-99a for subsequent functional studies where its activity was specifically manipulated in cortical neurons using LNA oligonucleotide technology, showing an effect in the growth of the developing axon (Fig1.b). Moreover, pathway analysis tools indicate that miR-99a is predicted to target molecular networks relevant for cellular growth and proliferation.

We are currently using different experimental models to address the role miR-99a in the formation of neuronal networks, including morphological (axon growth, synaptogenesis) and functional (microelectrode arrays) studies. This work is expected to provide new insights on the microRNA regulatory network that regulate the molecular pathways underlying neuronal connectivity in the central nervous system.

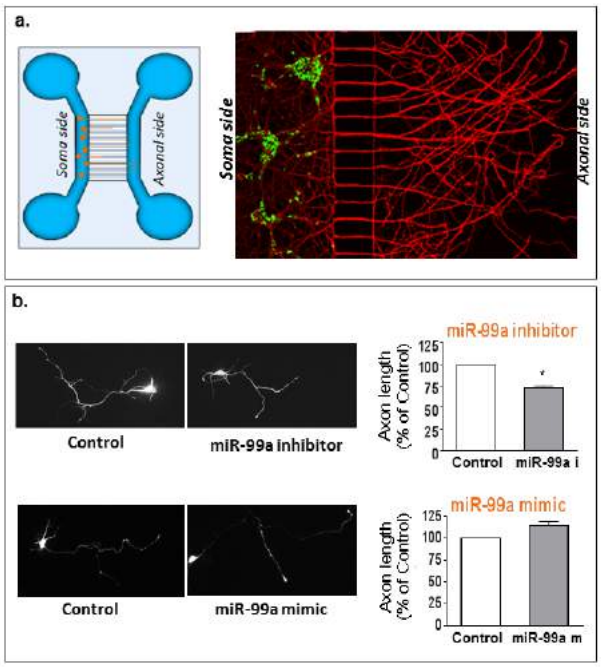


Figure 1.
a. Schematic representation (left) and immunofluorescence (right) images of the microfluidic culture model showing primary cortical neurons extending axons through microgrooves into the axonal compartment, thus allowing for the isolation of axons from their cells bodies (Acetylated tubulin - red, Otx-1 – green). **b. Effect of the manipulation of miR-99a levels in axonal outgrowth** of primary cortical cultures over development. The specific inhibition of endogenous miR-99a resulted in neurons bearing shorter axons (upper panel), whilst cortical neurons transfected with a mimic for miR-99a showed an increase in average axon length (Mean±SEM), thus suggesting a role for miR-99a in axonal outgrowth.

Contact email address: mbxrtr@nottingham.ac.uk
Poster number: P-W056
Theme: Neuronal, glial & cellular mechanisms

Use of D-Aspartate as a false gliotransmitter to investigate spontaneous glia-neuron signalling in the rodent barrel cortex

Authors: S. Antonio - *School of Life and Health Sciences Aston University*, D. Ursu - *Neuroscience Eli Lilly and Co*, R. Parri - *School of Life and Health Sciences Aston University*

Astrocytes show bidirectional communication with neurons, spontaneously releasing gliotransmitters (GTs) such as glutamate, ATP, and GABA that modulate synaptic and neuronal network activity. Various GT release mechanisms have been proposed, such as via calcium dependent vesicular exocytosis, excitatory amino acid (EAA) transporters, ion channels such as TREK1 and Bestrophin-1 (Best-1), and hemichannels. We have investigated the mechanisms of spontaneous NMDA receptor mediated slow inward current (SIC) generation in an enhanced EAA release model. Patch clamp recordings were conducted in layer 2/3 pyramidal neurons in rodent thalamocortical slices from animals at P10-P28 after pre-exposure to 100µM D-Aspartate. Slow-inward currents (SICs), defined as having an amplitude >20pA and rise time >20ms, were recorded. SICs were observed in the presence of TTX and pharmacological methods were used to characterise the mechanisms of EAA release. SICs still occurred in the presence of inhibitors of VGLUT1, hemichannels, temperature sensitive and volume regulated channels, or anion channels such as Best-1. Similarly, manipulation of internal calcium with the SERCA pump blocker cyclopiazonic acid, did not decrease SIC rate. Moreover, inositol 1,4,5-triphosphate (IP3) type-2 receptor knock-out mice which show decreased somatic astrocyte calcium transients, did not have a significantly different SIC rate compared to wild type animals. This indicates that SICs occur through a mechanism that is independent of IP3 mediated intracellular calcium release. Together, these results suggest that this enhanced astrocyte EAA release model is resistant to pharmacological blockade of individual efflux pathways.

Contact email address: antonisa@aston.ac.uk

Poster number: P-W057
Theme: Neuronal, glial & cellular mechanisms

AMPA receptor trafficking in DHPG-LTD occurs predominantly at synapses with a low probability of neurotransmitter release.

Authors: Thomas M Sanderson - *Physiology, Pharmacology and Neuroscience University of Bristol*, Sang Jeong Kim - *Department of Brain and Cognitive Sciences Seoul National University*, Graham L Collingridge - *Department of Physiology University of Toronto*

Information can be encoded in the brain due to the plastic nature of synapses. One form of synaptic plasticity is the long term decrease in synaptic strength termed long term depression (LTD) and this may be triggered by either N-methyl D-aspartate receptors (NMDARs) or group I metabotropic glutamate receptors (mGluRs). Here we have focussed on the mechanisms that underlie mGluR-LTD, a type of plasticity that has been implicated in spatial reversal learning and novel object recognition. This form of plasticity may be expressed by trafficking of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) and the AMPAR trafficking involved may occur in a specific pattern compared to that in NMDAR dependent LTD. For example, using a version of the GluA2 AMPAR subunit tagged with the pH sensitive fluorophore super ecliptic pHluorin (SEP-GluA2), we previously found that activation of group I mGluRs with dihydroxyphenylglycine (DHPG) resulted in enhanced variability of surface expression, whereas activation of NMDARs caused a decrease. Here we have further studied this phenomenon in organotypic hippocampal slices by investigating how AMPAR trafficking induced by DHPG varies as a function of probability of neurotransmitter release, P(r).

We biolistically transfected SEP-GluA2 in area CA1 and examined its fluorescence 3-5 days later. In untreated conditions SEP-GluA2 fluorescence was stable over a 30 min time period at 109 ± 16 % of baseline values. As previously reported NMDA application resulted in a significant decrease in SEP-GluA2 fluorescence to 63 ± 7 % and DHPG resulted in a more subtle decrease to 100 ± 16 %. We then measured the P(r) of synapses using the styryl dye FM 4-64 in combination with SEP-GluA2 expression. This approach revealed that DHPG induced trafficking of SEP-GluA2 occurred specifically at low P(r) synapses.
These results indicate that DHPG-LTD specifically targets less active synapses for postsynaptic downregulation. This may ensure that resources are not used unnecessarily to maintain underused synapses.

Contact email address: thomasmackleysanderson@gmail.com

Poster number: P-W058
Theme: Neuronal, glial & cellular mechanisms

Quantification of fast presynaptic Ca2+ kinetics using non-stationary single compartment model

Authors: Yulia Timofeeva - *Computer Science University of Warwick*, Dmitri A Rusakov, Kirill E Volynski - *Institute of Neurology UCL*

Fluorescence imaging is an important tool in examining Ca2+-dependent machinery of synaptic transmission. Classically, deriving the kinetics of free Ca2+ from the fluorescence recorded inside small cellular structures has relied on singe-compartment models of Ca2+ entry, buffering and removal. In many cases, steady-state approximation of Ca2+ binding reactions in such a model allows elegant analytical solutions for the Ca2+ kinetics in question. However, the fast rate of action potential (AP)-driven Ca2+ influx can be comparable with the rate of Ca2+ buffering inside the synaptic terminal. In this case, computations that reflect non-stationary changes in the system might be required for obtaining essential information about rapid transients of intracellular free Ca2+. Based on the experimental data we propose an improved procedure to evaluate the underlying presynaptic Ca2+ kinetics. We show that in most cases the non-stationary single compartment model provides accurate estimates of action-potential evoked presynaptic Ca2+ concentration transients, similar to that obtained with the full 3D diffusion model. Based on this we develop a computational tool aimed at stochastic optimisation and cross-validation of the kinetic parameters based on a single set of experimental conditions. The proposed methodology provides robust estimation of Ca2+ kinetics even when a priori information about endogenous Ca2+ buffering is limited.

Contact email address: y.timofeeva@warwick.ac.uk

Poster number: P-W059
Theme: Novel treatments & translational neuroscience

Docosahexaenoic acid reduces the sensorimotor neurological deficit after traumatic brain injury in mice

Authors: Adina Michael-Titus, Orli Thau-Zuchman, Rachael Ingram, Meirion Davies, Jordi Lopez-Tremoleda - *Centre for Neuroscience and Trauma, Blizard Institute Barts and the London School of Medicine and Dentistry, Queen Mary University of London*

Traumatic brain injury (TBI) can lead to long-lasting and life-changing neurological deficits. The deficit is a consequence of the secondary injury which develops in the aftermath of injury, and which expands the damaged area beyond the injury epicentre. The secondary injury can be targeted by neuroprotective agents. We have previously shown that the omega-3 fatty acid docosahexaenoic acid (DHA) has significant neuroprotective effects when acutely administered after traumatic spinal cord injury. The aim of our study was to explore the potential of this treatment in experimental TBI. Adult male mice were injured using a unilateral controlled cortical impact injury (CCI) and were monitored for sensorimotor impairment using the modified Neurological

Severity Score (mNSS), up to 28 days post-injury. DHA (500 nmol/kg) or saline were injected intravenously in CCI animals at 30 min after injury. Control animals received a craniotomy only. After completion of the behavioural experiments, the tissue was analysed using neuronal and non-neuronal markers. The results showed that the fatty acid led to a significant reduction in neurological deficit, which was already apparent in the first 3 days after injury.

The analysis of the tissue at 7 days after CCI showed that the DHA group had a significantly reduced lesion size and a reduced microglia and astrocyte activation. The injury induced a cell proliferative response, revealed by bromodeoxyuridine labeling in the perilesional area, and this response was amplified by DHA treatment. The fatty acid also led to a reduced tissue oxidation, as reflected by a lower 8-hydroxyguanosine level. The DHA-injected group displayed a much reduced accumulation of beta-amyloid precursor protein in the perilesional zone, indicating a reduced axonal injury. The results suggest that the acute DHA administration after injury has the potential to reduce the negative impact of severe concussion TBI, and the improved neurological outcome seen after acute treatment with this fatty acid is linked to early improvement in several tissue parameters.

Contact email address: A.T.Michael-Titus@qmul.ac.uk

Poster number: P-W060
Theme: Novel treatments & translational neuroscience

Identification of Neuropathic Pain Biomarkers in the Rat Spinal Nerve Ligation Model

Authors: Bethan Young - *Applied Sciences Centre for Biomarker Research, University of Huddersfield*, David Finn - *Department of Pharmacology & Therapeutics Centre for Pain Research, NUI Galway*, Patrick C. McHugh - *Applied Sciences Centre for Biomarker Research, University of Huddersfield*

Chronic neuropathic pain (NP) is a common yet poorly understood condition, with 20% of patients receiving treatment still experiencing moderate to severe pain. This ineffective use of healthcare resources is largely due to inaccurate diagnosis and inappropriate symptom management programmes. The development of objective diagnostic strategies requires robust biomarkers of NP to be identified, this could lead to more effective medications for pain management and its underlying pathologies. To this end, we aim to identify biomarkers of chronic NP by assessing the gene expression profiles of an animal model of NP. We will then ascertain their functionality as biomarkers in NP patient cohorts.

Dorsal horn tissue extracted form a Sprague Dawley rat spinal nerve ligation (SNL) model (30 days post-surgery, n=8) was used to gain a gene expression profile vs sham operated controls (n=8) following analysis using the Affymetrix Rat Transcriptome Array 1.0 and quantitative PCR. Genes with significant expression changes ($p<0.05$) were analysed using Ingenuity Pathway Analysis® software.

Our gene expression analysis revealed a subset of significant genes, including a subset of microRNA changes. These differentially regulated genes include those that influence inflammatory processes and apoptosis. For example, pro-apoptotic caspase 1 and caspase 4, chemokine receptor C-C motif 5 (Ccr5), and cluster of differentiation 4 (Cd4) are upregulated in SNL and highlights a potential pathway that could have implications in NP.

Validation of these findings in the gene expression profile of human blood samples will assess their clinical relevance. Molecules which demonstrate an active role in human NP have the potential to be developed into a biological measure for objective diagnostic tests, or as novel drug targets for improved pain management. Such developments could help to relieve the social and economic burden of NP by restoring patient health-related quality of life.

Contact email address: bethan.young@hud.ac.uk

Poster number: P-W061
Theme: Novel treatments & translational neuroscience

The role of synaptic scaffolding protein-Shank3 in brain inflammation after ischemic stroke

Authors: Chih Hao Yang, Hsing-Ni Li, Bo-Ru Huang, Cheng-Ying Hsieh, Joen-Rong Sheu - *Department of Pharmacology College of Medicine, Taipei Medical University*

Stroke, is the second leading cause of death in the world. There are two types of stroke which are ischemic stroke and hemorrhagic stroke. Ischemic stroke, which contributes to 87% of cases, is caused by the interruption or reduction of blood supply to the brain by blood clots and lead to lacking of regional blood flow. Damage of neuronal populations or reperfusion of blood flow after ischemic stroke may activate regional glial cells such as microglia and astrocytes which leads to the induction of inflammatory responses. Accumulating evidence by clinical or rodent studies has indicated that over-activated or dysregulated inflammatory events might be linked to poor prognosis after hypoxic challenge. Therefore, investigation of the regulatory mechanisms modulating the hypoxia induced inflammatory responses might provide valuable therapeutic directions for stroke.
Previous data from our laboratory indicated that Shank3 is differentially expressed in distinct species of mice and there is a significant positive correlation between the Shank3 expression levels with the severity of hypoxia induced phenotypes. Moreover, the expression of neuro-inflammatory molecules, such as iNOS, IL-6, IL-1β, and TNF-α were profoundly increased in the animals with higher levels of Shank3. So we postulated that if Shank3 might have some roles in regulating of hypoxia induced inflammatory responses. By using in vitro primary culture of three different cell types (neuron, astrocyte, and microglia), we provide evidence showing that isolated microglial cells are the major population of cells which responsible for the expression of inflammatory molecules after hypoxic challenge. Meanwhile, the production of inflammatory molecules by microglia can be profoundly enhanced by the conditioned medium obtained from hypoxic challenged neuron. However, such priming effects were significantly attenuated after we knockdown of Shank3 in neuron by lentiviruses. Our current study has provided strong evidence showing the critical role of Shank3 in communication between neuron and microglia that modulates downstream inflammatory events after hypoxic challenge. These findings may have the potential to provide a promising therapeutic strategy for ischemic stroke by targeting Shank3.

Contact email address: chyang@tmu.edu.tw

Poster number: P-W062
Theme: Novel treatments & translational neuroscience

Delivery of Mutated BDNF into the CNS using Gold Nanoparticles

Authors: Conor McQuaid - *STEM Open University & Midatech Pharma*, Prof. Ignacio Romero, Prof. David Male - STEM Open University

More than 95% of the drugs that could potentially treat neurological diseases do not cross the endothelial cells of the blood brain barrier (BBB), and one of the fastest growing areas of research to overcome this barrier is the use of nanocarriers.

Gold nanoparticles have a number of unique properties that make them useful as nanocarriers, including stability, and low cytotoxicity/immunogenicity. Results from our group have previously demonstrated that they can cross in vitro models of the human BBB and can cross endothelium and enter cells of the CNS, following intravascular infusion in rats.

One of the major factors affecting the ability of these nanoparticles to cross the BBB is their coating. We have examined the rate at which 2nm gold nanoparticles with a covalently linked glycan coat can cross human brain endothelium and have selected 3 nanoparticle coating options which will be used as base nanocarriers.

We aim to attach BDNF (brain derived neurotrophic factor) a cytokine which has shown positive results in the treatment of neurodegenerative disorders, but its inability to cross the BBB has limited its development.

We have altered a plasmid encoding BDNF to insert a C-terminal cysteine residue, allowing covalent attachment to the gold nanoparticle. The modified BDNF, synthesised in transfected cells, is detectable by immunoassay and is currently being tested for biological function. Methods for attaching BDNF to the nanoparticles and evaluating their biological function and their potential to carry cytokine into the CNS, will be discussed.

Contact email address: conor.mcquaid@open.ac.uk

Poster number: P-W063
Theme: Novel treatments & translational neuroscience

Functional Endpoint Assays to Assess Neurotoxicity with Human iPSC-derived Neurons

Authors: Giorgia Salvagiotto - *Life Science Cellular Dynamics Intl*

Human cell types differentiated from induced pluripotent stem cells (iPSC) offer a unique source of cellular material for toxicity screening. Several examples have been presented on the use of iPSC-derived cardiomyocytes and hepatocytes, for example, in safety toxicology studies. Equally important is comparative neurotoxicity assessment in neuronal cell types for safety toxicology and uncovering molecular mechanisms underlying excitotoxic cell death pathways. Advances in iPSC technology provide access to previously unattainable cell types from the human brain opening new opportunities to address the shortcomings and limitations of rodent primary cells and immortalized cell lines.

Here we present the neurotoxic effects of the excitatory neurotransmitter glutamate and related compounds across a panel of cell types, including iPSC-derived GABAergic and glutamatergic cortical neurons, as well as midbrain dopaminergic neurons. For comparison, the cytotoxicity of a broad spectrum kinase inhibitor, staurosporine (STS), was also evaluated. To achieve robust signals across these different iPSC-derived neuron types, we have optimized the cell culture protocols (i.e., media, time in culture, cell plating density, etc.). Under the various conditions tested, we observed differential responses for glutamatergic compounds (e.g. glutamate, NMDA, AMPA, and kainic acid) versus STS, suggesting the toxicity responses were due to excitotoxic effects of neuronal synaptic receptors and not other mechanisms. Importantly, toxicity induced by glutamate could be reversed with antagonists of the AMPA and NMDA receptors, DNQX and D-AP5, respectively. We also highlight examples using human iPSC-derived neurons on multi-electrode arrays (MEA) to assess the effects of both developmental and environmental neurotoxicants.
Overall, these iPSC-derived neurons exhibit functional glutamate pathways that respond appropriately to known agonists and antagonists, thus providing biologically relevant models for identifying emerging targets for excitotoxicity research. Together with the developmental and environmental toxicity studies, these data establish a clear utility for each of these cell types in neurotoxicology

Contact email address: gsalvagiotto@cellulardynamics.com

Poster number: P-W064
Theme: Novel treatments & translational neuroscience

Metformin attenuates morphine tolerance and potentials morphine effects in a mouse model of neuropathic pain.

Authors: Amal Alsubayiel, JoãoPaulo Ferreira Bertacchi, Elizabeth Middleton - *School of Medicine, Pharmacy and Health Durham University*, Sam Eldabe - *Department of Pain and Anesthesia The James Cook University Hospital, Middleborough, UK*, Ilona Obara - *School of Medicine, Pharmacy and Health Durham University*

Opioids, like morphine, remain the mainstay of clinical analgesia. However, the clinical usefulness of opioids is restricted by therapeutic desensitization (tolerance) resulting from prolonged opioid administration and low opioid effectiveness in neuropathic pain. These suggest a pressing need for the identification of new strategies to improve efficacy of opioid-based treatments. Recently, it has become clear that the mammalian target of rapamycin complex 1 (mTORC1), a kinase which controls protein synthesis, regulates nociceptor sensitivity and modulates opioid efficacy. However, direct mTORC1 inhibitors are only used in limited clinical indications due to adverse effects. Thus, this study explored for the first time the effect of the widely used anti-diabetic drug metformin that inhibits mTORC1 through activation of the 5' adenosine monophosphate-activated protein kinase (AMPK) on the development of morphine tolerance in naïve neuropathic mice. Specifically, administration of morphine to both naïve (20 mg/kg, i.p.) and neuropathic (40 mg/kg, i.p., spared nerve injury model - SNI) adult male C57BL/6J mice (n=5-6) mice resulted in tolerance to its analgesic effect after 6-8 days of morphine treatment. When metformin (200 mg/kg, i.p.) was administered 24 hours before each morning morphine injection tolerance did not develop as measured by the tail-flick test, von Frey and acetone tests. Also, a single metformin dose injected on day 8-9 in morphine tolerant naïve and SNI mice fully restored the analgesic effect of morphine. In addition, when metformin was injected in combination with morphine (3, 10, 20 mg/kg, i.p.) in SNI mice it potentiated dose-dependently analgesic effect of morphine in mechanical and cold hypersensitivity tests. Our parallel studies using the direct mTORC1 inhibitor CCI-779 (25 mg/kg, i.p.) showed that these effects were attributed to mTORC1 inhibition. This mechanism was confirmed by Western blotting showing inhibition of one of mTORC1 downstream targets P-p70 S6 kinase in the dorsal spinal cord after metformin treatment. Together, our results support the idea that targeting mTORC1 the widely used drug may offer a novel avenue for the improvement of opioid therapy in humans, particularly when prolonged opioid treatment is required.

Contact email address: ilona.obara@durham.ac.uk

Poster number: P-W065
Theme: Novel treatments & translational neuroscience

Dose-dependent neuroprotection of IOX3 and GSK1278863 in PC12 cells following 24 hour oxygen and glucose deprivation

Authors: James Wilson - *School of Pharmacy/ISTM Keele University*

Ischaemic pre- and post- conditioning induce neuroprotection in various models of stroke and neuronal injurious. It is proposed that preconditioning protection can also be achieved with drugs that cause hypoxia-inducible factors (HIF) to accumulate in cells.

Herein, the neuroprotective effects of two small molecule HIF prolyl hydroxylase (PHD) inhibitors (GSK1278863 and IOX3) were investigated in the neuronal PC12 cell line whilst implementing combined 24 hours oxygen-glucose deprivation (OGD). OGD insulted PC12 cells were administered drug doses of 10 and 100 µM: immediately prior to OGD treatment; or 24 hours prior to OGD (pre-conditioned). OGD experiments were carried out in the hypoxic chamber at 1% O2, 5% CO2 and 37°C for 24 hours, using glucose-free medium. Cell survival/death and viability were then measured by lactate dehydrogenase (LDH) release and MTT assays, while gene expression of HIF-1α and numerous HIF downstream genes were analysed with qRT-PCR.

LDH release from cells was significantly higher following 24 hour OGD than those in normoxic conditions (14.1+1.1% vs 60.3+4.3, $p<0.05$). Likewise, cell viability was significantly reduced when compared to controls (30.7%). Additionally, a 6 hour OGD pre-treatment significantly reduced LDH release compared to untreated cells (50.6±3.1% vs 58.6±2.6%, $p<0.05$). Similarly, pre-treatment, with 100 µM IOX3 or GSK1278863 significantly reduced LDH release compared to vehicle (1% DMSO) only treatment (IOX3: 58.3±5.2% vs 87.9±5%, $p<0.05$; GSK1278863: 62.4±6.4% vs 87.9±5%, $p<0.05$). Conversely, doses of 10 µM did not evoke significant protective capabilities. Moreover, LDH release did not significantly reduce in cells treated with IOX3 and GSK1278863 immediately before OGD compared to the vehicle. Finally, gene expression analysis illustrated significant upregulation of PHD2 and PDK in PC12 cells pre-treated with 100 µM IOX3, while 100 µM GSK1278863 also significantly upregulated PHD2 in addition to GLUT1 and EPO. HIF-1α gene expression however was not altered following either treatment.

In conclusion, IOX3 and GSK1278863 mediate dose-dependent neuroprotection when administrated in preconditioning, correlating with upregulation of a number of HIF downstream gene expressions.

Contact email address: j.wilson1@keele.ac.uk

Poster number: P-W066
Theme: Novel treatments & translational neuroscience

A self-administered, non-medical intervention to identify and improve cognitive issues in populations across a range of ages and health conditions

Authors: Keiron Sparrowhawk - *CEO MyCognition*, Martina Ratto, Brent Cliveden - *Research MyCognition*, John Harrison - *Research Metis Cognition*

Rationale: Cognitive issues are common in all ages of the population and are known to be related to health, personal habits and home/work environment. Cognitive impairment is often associated with major psychiatric disorders, medical conditions, specific learning and behaviour disorders, and neurodegenerative diseases. However poor cognitive health will also occur within the general population, without a neuropsychiatric diagnosis, due to chronic stress, unhealthy life habits, or early-stage diseases. To date it has proven difficult to detect these conditions early enough to investigate preventative or treatment interventions. The potential of these interventions could be based on brain plasticity, e.g., through adaptations of the environment.

Method: An on-line, self-administered tool has been developed. This is a neuropsychological assessment of processing speed, attention, working memory, episodic memory, and executive function. The test produces a domain-specific score plus a measure of overall cognitive health. The assessment scores are automatically linked to a personalised cognitive training program. The training is embedded in an engaging and challenging video game, which trains holistically, but targets the user's weaker domains with greater intensely. It is recommended to use the training program 90 minutes per week at least for 8 to12 weeks, and to initially use the assessment tool to monitor progress every 4 weeks.

Results: The program has been successfully adopted in clinical trials, and in real-world studies in schools and businesses. The assessment tool could identify people with overall cognitive health problems or issues related to a specific domain. The training game has been shown to produce positive improvements in cognitive function in groups following the training program compared with control groups.

Conclusions: The software described is being used as a time- and cost-effective innovative solution to target cognitive issues alongside medical treatments or where clinical interventions are not required. Current studies are targeting a range of health conditions involving mainstream students and those with learning difficulties, working adults, troubled families, and the elderly.

Contact email address: keiron.sparrowhawk@mycognition.com

Poster number: P-W067
Theme: Novel treatments & translational neuroscience

Temporal lobe white matter fibre delineation in refractory temporal lobe epilepsy with and without hippocampal sclerosis

Authors: Lucy Lisanti, Barbara Kreilkamp - *Institute of Translational Medicine University of Liverpool*, Kumar Das, Udo Wieshmann - *Neurology The Walton Centre NHS Foundation Trust*, Anthony Marson, Simon Keller - *Institute of Translational Medicine University of Liverpool*

White matter fibre bundles can be reconstructed using diffusion tensor imaging (DTI) and tractography. Temporal lobe white matter fibre bundles are frequently reported to be abnormal in DTI studies of patients with temporal lobe epilepsy (TLE) and associated hippocampal sclerosis (HS). In the present study, we sought to delineate and assess the diffusion characteristics of two important temporal lobe white matter tract bundles in patients with TLE recruited into this study as non-lesional cases.

3D T1-weighted and DTI MRI sequences on 3 Tesla GE system for 40 neurologically healthy controls and 24 patients with non-lesional TLE (16 left TLE, 8 right TLE). Whole brain tractography and delineation of the uncinate fasiculus (UF) and parahippocampal white matter bundle (PWMB) was carried out using Diffusion Toolkit and TrackVis (Figure. 1.). Mean fractional anisotropy (FA) and mean diffusivity (MD) values were obtained for each bundle in each hemisphere. FA and MD were compared between patient and control groups, and correlated with clinical data.

Kruskal-Wallis and post-hoc testing revealed significantly increased MD in the left UF ($p=0.01$), right UF ($p=0.003$) and right PWMB ($p=0.02$) in patients with left TLE relative to controls. An increased seizure burden (log(duration of epilepsy x seizure frequency per week)) correlated with a decrease in FA of the ipsilateral ($r=-0.50$, $p=0.02$) and contralateral ($r=-0.50$, $p=0.05$) UF. An earlier age of onset correlated with a decrease in FA in the contralateral UF ($r=0.43$, $p=0.04$) and contralateral PWMB ($r=0.41$, $p=0.05$). A longer duration, when corrected for age, correlated with a decrease in FA of the ipsilateral ($r=-0.52$, $p=0.009$) UF, contralateral ($r=-0.56$, $p=0.005$) UF, ipsilateral ($r=-0.45$, $p=0.03$) PWMB and contralateral ($r=-0.43$, $p=0.03$) PWMB; and an increase in MD of the contralateral UF ($r=0.47$, $p=0.02$). HS was diagnosed in eight patients who were previously deemed to be non-lesional.

The UF is particularly vulnerable to pathological alterations in patients with non-lesional TLE. This abnormality is compounded by an earlier age of onset, a longer duration of epilepsy, and increased epilepsy burden. This data indicate that the abnormality is present regardless of the presence of HS.

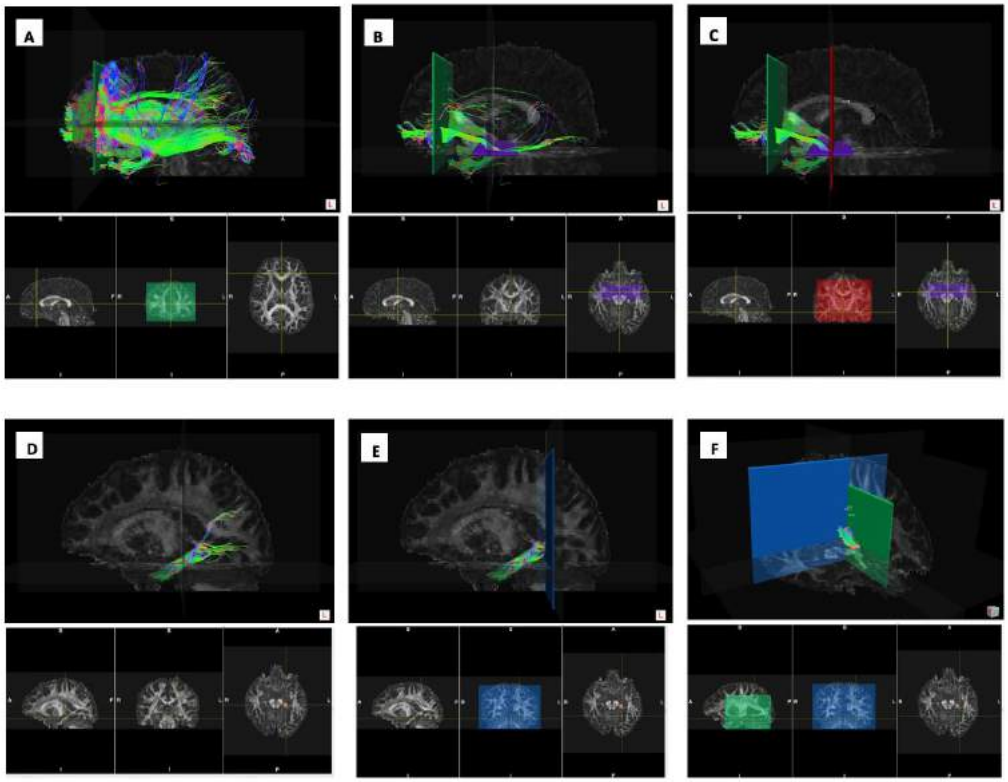


Figure. 1. **Delineation of UF (A-C) and PHWM (D-F) using regions of interest (ROI).** Colours of fibres indicate directionality of fibres: green = rostral-caudal, blue= dorsal-ventral, red = medial-lateral. **A** = Placement of 'AND' ROI 1 (green) on coronal slice. **B** = Placement of 'AND' ROI 2 (purple) on axial slice. **C** = Placement of 'NOT' ROI 3 (red) on coronal slice. **D** = Placement of 'AND' ROI 1 (orange) on axial slice. **E** = Placement of 'NOT' ROI 2 (blue) on coronal slice. **F** = Placement of 'NOT' ROI 3 (green) on sagittal slice.

Contact email address: lucylisanti@gmail.com

Poster number: P-W068
Theme: Novel treatments & translational neuroscience

Promising insight into use of Constant Therapy tool in rehabilitation after traumatic brain injury

Authors: Michelle Vermeulen - *Therapies Team Nottingham Brain Injury Rehabilitation and Neurological Care Centre*

There has been a growing number of research-led cognitive tools to assist with rehabilitation following neurological injury. This preliminary investigation explores the use of an individualised application, Constant Therapy (Constant Therapy Inc., 2016), when used solely in a clinical setting, in comparison to previous studies which examine its use both in clinical and domestic setting. Significant correlations were found between accuracy and latency improvements when these were seen across both cognitive and language-based tasks. This is a promising initial exploration of the outcomes seen when using this software as part of a rehabilitation treatment programme following traumatic brain injury.

Contact email address: Michelle.Vermeulen@student.shu.ac.uk

Poster number: P-W069
Theme: Novel treatments & translational neuroscience

Effect of Pulsed Electromagnetic Field (PEMF) on the Regeneration of Crush-injured Mental Nerve

Authors: Na Ri Seo - *Dental Science Seoul National University of School of Dentistry*, Sung Ho Lee - *Dental Research Institute Dental Research Institute*, Kyung Won Ju - *Oral & Maxillofacial Surgery Seoul National University Dental Hospital*, Jong-Ho Lee - *Dentistry Seoul NatiSeoul National University of School of Dentistry*

Purpose. In previous studies, difference was found in neurotrophic factor expression between Pulsed electromagnetic field (PEMF)-treated mesenchymal stem cells and non-treated cells. Therefore, this study aims to evaluate nerve regeneration when each cell was injected into SD rats with mental nerve crush injury.

Material & Method. MSCs were collected from Sprague-Dawley rats of 5-weeks-old. MSCs were confirmed by using CD29 and CD105. MSCs were divided into two groups of which one was exposed to PEMF in the condition of 50Hz, 10Gauss, 1hr/d for 5, 7, 10,

14 days, and not for the other group. S100, GFAP, NGF, BDNF expression level was compared through RT-PCR. SD rats were divided into 8 groups in vivo: Sham, Sham_PEMF, PBS, PBS_PEMF, MSC, MSC_PEMF, PMSCs, PMSC_PEMF. The left mental nerve was given crush injury and MSCs, PMSCs (1x106/5$\mu\ell$) were injected into the nerve. The rats were exposed to PEMF on the same condition as in vitro, one day post-surgery for 14 days. At one and two weeks post-surgery, nerve regeneration of each group was evaluated through sensory test using filaments, histomorphometry and dil-labeled neurons.

Result. The MSCs group that was exposed to PEMF for 10 days was higher in GFAP, NGF, BDNF expression level compared to the group that was not. Statistical significance was especially seen in NGF and BDNF. Nerve regeneration in all groups was enhanced with PEMF exposure in vivo. The group that was exposed to PEMF after PMSCs injection was the best in nerve regeneration in Gap and Different score of sensory test. The result of histomorphometric analysis and retrograde labelling was higher in all the PEMF-treated groups. Especially, the group that was exposed to PEMF after PMSC injection showed a highest result. This supports the hypothesis that PEMF improves nerve regeneration and PMSCs-PEMF group is the most effective in regeneration ability.

Conclusion. This study confirms that applying PEMF in vitro and in vivo is effective in enhancing regeneration of damaged nerves.

Contact email address: tj0943@snu.ac.kr

Poster number: P-W070
Theme: Novel treatments & translational neuroscience

Determining whether sex influences the neuroprotective effectiveness of progestins following in vitro ischaemic cell death.

Authors: Raeed Altaee - *Neuroscience, Psychology and Behaviour University Of Leicester* & Department of Physiology and Pharmacology, University of Karbala, Iraq, E Chrysanthou, M Trotman-Lucas, CL Gibson - Department of Neuroscience, Psychology and Behaviour, University of Leicester, UK

There is increasing evidence that innate differences in stroke risk and pathological outcome exist between men and women. In addition, the contribution of hormonal influences on the outcome after ischaemic stroke are well recognized and steroid hormones, such as progesterone, are potential neuroprotective factors following ischaemic stroke. In the current study, sex-specific ischaemic models using organotypic hippocampal sliced cultures (OHSCs) were used to test whether sex had any effect on the neuroprotective effectiveness of progestins under ischaemic conditions. OHSCs, prepared from sexed pups (postnatal day 6-9), were exposed to oxygen and glucose deprivation (OGD) in order to mimic ischaemia and stained with propidium iodide (PI) and Hoechst to visualise (and measure) the amount of ischaemic cell death following steroid hormone administration. In both sexes, treatment with progesterone (PG) and allopregnanolone (Allop) significantly ($P < .0001$) reduced the amount of cell death following 4 hours of OGD while treatment with medroxyprogesterone acetate (MPA) significantly reduced the amount of cell death in females but had no effect on males. A post-hoc analysis revealed that cell death was significantly ($P < .0001$) decreased following treatment with 100 nM PG and Allop in both sexes. Interestingly, there was a significant ($P < .0001$) reduction in cell death in female-derived OHSCs compared to male-derived OHSCs following 4 hours exposure of OGD and exposure to PG, Allop or MPA treatment. Such findings will be useful in examining the interaction of steroid hormones with specific elements of the cell death pathways.

Contact email address: ra348@le.ac.uk

Poster number: P-W071
Theme: Novel treatments & translational neuroscience

Deep brain stimulation of the vmPFC attenuates both positive and negative affective biases in rats.

Authors: Sarah Stuart, Emma Robinson - *Physiology, Pharmacology and University of Bristol*

Subcallosal cingulate gyrus (SGC) deep brain stimulation (DBS) has antidepressant effects in humans. Our previous work in rats using a novel affective bias test (ABT) suggests that the attenuation of negative biases may contribute to antidepressant efficacy. The present study assessed whether electrical stimulation of the ventromedial prefrontal cortex (vmPFC) attenuates affective biases in rats.

16 male Lister hooded rats were implanted with left unilateral bipolar electrodes into the vmPFC prior to ABT training. The ABT uses a bowl-digging task where rats encounter two independent positive experiences (finding food reward in a specific digging

substrate). Treatment or control is administered prior to the experience, and the absolute reward value is kept consistent across all sessions. Affective bias is quantified in a preference test where both rewarded substrates are presented together and the rats' choices recorded over 30 randomly reinforced trials. All animals underwent pairing sessions where they received either corticosterone (cort:10mg/kg, s.c.) vs. vehicle to induce a negative affective bias, or the antidepressant venlafaxine (vfx:3mg/kg, i.p.) vs. vehicle to induce a positive bias. Electrical stimulation (200µA, 130Hz, 90µsec) was administered for 5 min before and throughout preference testing using a within-subject counterbalanced design. Sham treated animals received no stimulation. The effect of stimulation on reward valuation was tested in a 2 pellet vs 1 pellet study which has previously been shown to induce a bias towards the higher value substrate.

Stimulation of the vmPFC significantly attenuated cort-induced negative affective bias ($t14=3.57$, $p=0.003$) but only tended to reduce vfx-induced positive bias ($t14 = 1.79$, $p=0.09$) compared to sham treatment. Stimulation had no effect on positive bias induced by an increase in reward value.

These data suggest that DBS has a non-specific effect on affective biases as it attenuates both positive and negative bias through disruption of prefrontal function. However, the tendency for a greater influence on negative affective bias may contribute to the overall antidepressant efficacy of DBS. The data also suggest the effects of DBS on affective bias occur independently of a deficit in reward valuation.

Contact email address: pmsas@bristol.ac.uk

Poster number: P-W072
Theme: Novel treatments & translational neuroscience

Ethosuximide and neurodegeneration: Discovering novel neuroprotective compounds and disease-modifying targets

Authors: Shi Quan Wong, Alan Morgan - *Cellular and Molecular Physiology University of Liverpool*

The significant socioeconomic burden of neurodegenerative disorders is greatly attributed to an absence of cures and effective treatments, and is expected to exacerbate with the predicted growth of the global ageing population and consequential rise of age-associated neurodegenerative disorders. The antiepileptic drug (AED) ethosuximide was previously shown to ameliorate neurodegenerative phenotypes across several Caenorhabditis elegans and rodent neurodegeneration models, making it a promising candidate for repurposing as a general treatment for neurodegeneration. However, it has a range of associated side effects, unknown neuroprotective efficacy, and an unclear molecular mechanism of action despite being an established AED. With the aim of developing more potent neuroprotective compounds with reduced side effects using ethosuximide as a starting scaffold, chemistry approaches were employed to facilitate the selection and synthesis of compounds with structural similarity to ethosuximide. Selected compounds were screened in a C. elegans pentylenetetrazol (PTZ)-induced model of epilepsy, which identified the most potent one for subsequent assessment of its neuroprotective properties in a C. elegans neurodegeneration model of amyotrophic lateral sclerosis (ALS). Findings demonstrated a protective effect of the compound on neurodegenerative phenotypes by amelioration of locomotion defects and extension of the shortened lifespan of the model. Furthermore, the compound directly protected against neurodegeneration in the model by reducing the number of breaks and cell body losses in the GABAergic motor neurons. Most importantly, µM concentrations of the compound exhibited comparable neuroprotection with an optimal mM concentration of ethosuximide, strongly showing enhanced potency of the compound in comparison to ethosuximide.

Contact email address: wongsq@liverpool.ac.uk

Poster number: P-W073
Theme: Novel treatments & translational neuroscience

Acute and Repetitive Fronto-Cerebellar tDCS Stimulation Improves Mood in Non-Depressed Participants

Authors: Simon Newstead - *Psychology Swansea Universit*

Background: Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique which enables selective inhibition or excitation of neuronal structures, and has previously demonstrated potential in as a therapeutic intervention in the treatment of mood disorders. Prior studies have predominately focused on stimulation of the PFC, and have achieved varying degrees of success regarding elevation of positive mood in healthy individuals. However, the Cerebellum (Cb) has an increasingly

recognized role in emotion, affective state and the presentation of some psychopathologies. As such, tDCS research into mood modulation needs to expand beyond conventional PFC focused paradigms.

Method: Using a novel stimulation montage (left dlPFC anode, right Cb = cathode), and a single blind, pre-test/post-test design, we assessed changes in mood within healthy participants in response to acute stimulation (n = 45) and 3 repeated stimulations delivered bi-daily (n = 23). In a second experiment we then investigated the influence of reversed polarity upon alterations mood in response to acute stimulation (n = 25) and repeated stimulation (n = 11).

Results: Within both active conditions elevated mood was observed following acute and repeated fronto-cerebellar stimulation, of which the latter displayed a progressive elevation of mood. No change was noted in either single or repeated stimulations for the sham condition.

Conclusion: Fronto-cerebellar tDCS stimulation advantageously influences mood in healthy participants, with an accumulative and potentiated effect following successive stimulations. Fronto-cerebellar stimulation may provide a novel therapeutic adjunctive or pre-emptive intervention in stress related disorders and certain psychopathologies.

Contact email address: 882183@swansea.ac.uk

Poster number: P-W074
Theme: Novel treatments & translational neuroscience

Probabilistic framework simulating artificially-induced neural plasticity by a bidirectional Brain-Computer-Spinal Cord Interface

Authors: Stefano Vrizzi - *School of Biomedical Sciences University of Leeds*

Brain-Computer-Interfaces (BCIs) are a family of devices that process recorded brain activity to perform a desired output. Recent development of Bidirectional Brain-Computer Interface (BBCI), neural implants that not only record single-neuron activity at precise spike-time resolution, but also stimulates neuronal sites, open the door to direct interaction with the dynamics of neural circuits in the brain and in the nervous system at large. Specifically, Bidirectional-Brain-Computer-Spinal Cord Interfaces (BBCSIs) are implemented to record motor cortex (MC) activity and stimulate spinal cord (SC) sites to promote rehabilitation following spinal cord injury (SCI). The neurochip stimulation aims at triggering neural plasticity to restore disrupted pathways by exploiting Spike-Timing Dependent Plasticity (STDP) rules.

In a probabilistic model that we numerically simulate, MC and SC were represented by excitatory and inhibitory neurons, which were recurrently connected according to set connectivity probabilities schematising the corticospinal tract (CST). We investigated how spike-triggered stimulation protocols changed mean synaptic strength of existing excitatory synapses through a simple multiplicative STDP rule. We run different simulations stimulating either a group of neurons in MC or SC, or both, after set delays from the time of spiking of a recording neuron. Results were qualitatively consistent with previous computational and experimental findings. As we hypothesised, synapses strengthened between recording group and stimulated groups, as well as between stimulated groups. We also explored SCI by testing a double-site stimulation protocol, finding that mean synaptic strength may evolve in time depending on CST connectivity. These simulations highlight the potential of a double-site stimulation protocol in eliciting plasticity along descending pathways.

Contact email address: bs13s2v@leeds.ac.uk

Poster number: P-W075
Theme: Novel treatments & translational neuroscience

The study of electrophysiological mechanism in central dopaminergic neurons on the Depression induced by chronic neuropathic pain

Authors: Xiechuan Weng - *Department of Neurobiology & State Key Laboratory of Proteomics Institute of Basic Medical Science*

Objective: To explore the underlying electrophysiological mechanism of depression induced by chronic pain in dopaminergic neurons in midbrain ventral tegmental area (VTA) of rats.

Methods: we established the chronic neuropathic pain rats by spared nerve injury (SNI), the mechanical allodynia test and depressive-like behaviors such as open-field text, sucrose preference and forced swim text are detected on the day of 0, 7, 14, 28, 42 and 56 after surgery, then we use the Multichannel Acquisition Processor (MAP) system to record the firing activity of neurons in VTA in both control rats and depression rats.

Result: ① Comparing to sham rats, the paw withdrawal mechanical threshold of SNI Rats decreased significantly ($P<0.01$) ② According to depression-related behavioral test, SNI rats showed significant difference in open field text, sucrose preference, focus swim text comparing with Sham rats ($P<0.01$). ③ The firing rate and burst activity of dopaminergic neurons in midbrain ventral tegmental area are increased in depression rats compare to sham rats （$P<0.05$） ④ the HCN2 expression was increased in the VTA area of the SNI rats when compared with the sham rats.

Conclusion: The changes of the firing activity of dopaminergic neurons in midbrain ventral tegmental area might be contribute to the depression induced by the chronic neuropathic pain, which might be related with the increase of HCN2 expression.

Contact email address: wengxc2000@hotmail.com

Poster number: P-W076
Theme: Neurodegenerative disorders & ageing

Depression in a preclinical mouse model of Alzheimer's disease: a hedonic deficit not mediated by hippocampal dysfunction

Authors: Adam Brelsford - *School of Psychology Cardiff University*, Jasmine Clarkson - *Institute of Neuroscience Newcastle University*, Jessica Hall, Charles Evans, Dominic Dwyer, Mark Good - *School of Psychology Cardiff University*

Beyond memory impairment, which is the cardinal sign of Alzheimer's disease, patients often experience neuropsychiatric symptoms such as depression. Depression in Alzheimer's disease has been associated with increased mortality, a worsening of neuropathology and a more rapid cognitive decline. The protein β-amyloid, thought to be a key driver of disease pathology and impaired cognition in Alzheimer's disease, also has potential links with depression symptoms. Thus, animal models of Alzheimer's disease which recapitulate amyloid dysfunction are useful for exploring the nature of the relationship between amyloid dysfunction and depression. In addition, lesion studies can help determine whether brain structures damaged in Alzheimer's disease are likely to relate to depressive symptoms.

Aged (10 – 12 month old) Tg2576 mice (expressing a human APP genetic mutation found in familial Alzheimer's disease) had their licking microstructure examined when consuming 4% and 16% sucrose solutions. Tg2576 mice displayed a lower mean lick cluster size than their wild type counterparts, indicating a blunting of the hedonic response of Tg2576 mice in response to palatable sucrose. Beyond this effect, Tg2576 mice did not display the usual lick cluster size increase between 4% and 16% sucrose. These indications of impaired hedonic processing reflect a phenotype analogous to the anhedonia seen in human cases of depression.

The hippocampus is both critical for memory function and a major site of pathology in Alzheimer's disease. In addition, the amyloid dysfunction seen in aged Tg2576 mice is particularly pronounced in this brain region. To investigate whether hippocampal damage produces affective changes, a cohort of C57BL/6 mice were given either hippocampal or sham lesions. An examination of licking microstructure when consuming 4% and 16% sucrose solutions revealed no alteration in hedonic responding; both lesioned and sham-lesioned mice showed comparable lick cluster sizes at each concentration, and the typical increase in lick cluster size between concentrations. These experiments suggest that the biological processes leading to depression in Alzheimer's disease are unlikely to directly involve the hippocampus.

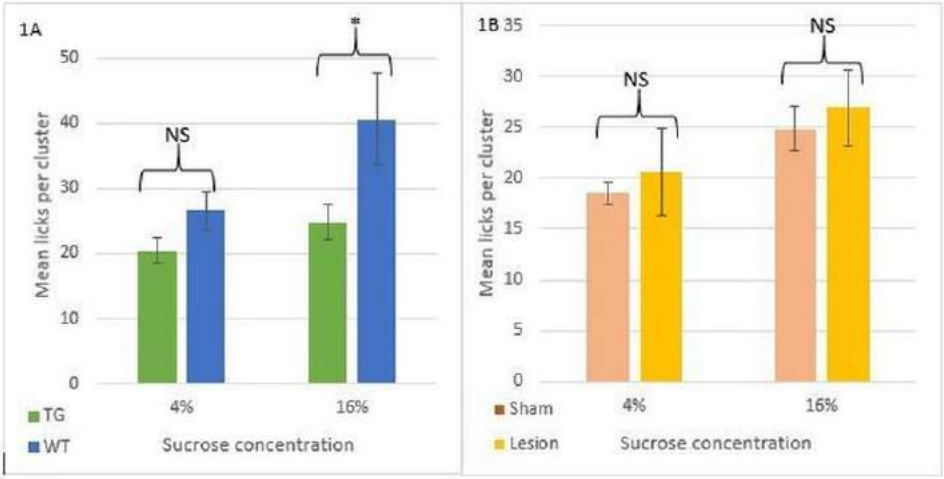


Figure 1. Mean number of licks per cluster at 4% and 16% w/w sucrose solutions. A: Tg2576 mice (TG, n=19) and wild type controls (WT, n=18). B) Hippocampal lesioned (lesion, n=10) and sham lesioned mice (sham, n=12). NS = not significant,* = p<.05.

Contact email address: BrelsfordAR1@cardiff.ac.uk

Poster number: P-W077
Theme: Neurodegenerative disorders & ageing

Evaluation of a novel peptide's bioactivity and its blockade via novel compounds using optical imaging: implications for neurodegenerative disorders

Authors: Alastair Munroe - *School of Physiology, Pharmacology and Neuroscience University of Bristol*, Scott Badin, Susan Greenfield - *Neuro-Bio Ltd. Neuro-Bio Ltd.*

Ever since Alois Alzheimer first characterised the presence of amyloid plaques (Aβ) and neurofibrillary tangles within a post mortem study of a dementia patient, vast amounts of work have been undertaken to ascertain the origin of these pathological markers, and also to try to develop a viable treatment for patients that have been diagnosed. In recent years, it has been hypothesised and later verified that a peptide, derived from acetylcholinesterase (AChE) has the potential to facilitate cellular mechanisms linked to AD, such as increased levels of phosphorylated glycogen-synthase-kinase-3, decreases amyloid precursor protein levels, and increases both Aβ and phosphorylated tau levels (Garcia-Ratés et al., 2016).
Using voltage sensitive dye imaging, this study investigates the effects of a synthetic version of this peptide on rat brain slices, containing the basal forebrain, a key site of degeneration in AD. Such a preparation allows the visualisation of sub-second neuronal networks, known as assemblies, which serve as an indicator for functional neuronal activity.
Here, this study shows that application of AChE-derived peptide is able to robustly modulate activity within the basal forebrain with these distinct directional effects being negatively correlated with baseline network activity. In order to investigate the potential for pharmacological intervention for this peptide, two blockers were used; NBP14, a cyclised variant of AChE-peptide, that has been previously shown to block the actions of its linear counterpart (Garcia-Ratés et al., 2016, Badin et al., 2016) and Tri02, a new linear peptidomimetic. Both blockers were able to reduce the effects of AChE-peptide, however upon comparison, Tri02 was shown to be less effective than NBP14 at blocking these modulatory effects.
These observations thus highlight: 1. the characterisation of the actions of AChE-peptide and its role in imparting dysfunctional activity within a key brain region linked to AD related cognitive decline and 2. give insights into the prospective pharmacological action, future studies might take to develop a successful treatment.

Contact email address: am13907@my.bristol.ac.uk

Poster number: P-W078
Theme: Neurodegenerative disorders & ageing

Acyl-ghrelin, a regulator of the adult hippocampal stem cell niche and biomarker of dementia in humans.

Authors: Amanda Hornsby, Alison Yarnall, Lisa Saksida, David Burn, Zane B Andrews, Jeffrey S Davies, *Institute of Life Science, College of Medicine Swansea University*

The dentate gyrus (DG) is a neurogenic niche in the adult mammalian brain where new neurones are formed from neural stem/progenitor cells (NSPCs) throughout life. These new adult born neurones play a key role in learning and memory. Calorie restriction (CR) has been shown to modulate the DG and improve cognitive function, albeit via unknown mechanisms. The gut hormone, acyl-ghrelin (AG), is elevated during CR and travels via the blood to the brain where it binds to its receptor, GHSR, in the hippocampus.

Initially, adult male GHSR-eGFP mice were used for phenotypic characterisation of GHSR in brain. Immunofluorescence and confocal microscopy was performed with anti-GFP antibody along with antibodies to; type I (Nestin+) and type II (Sox2+) NSPCs, proliferating cells (Ki67+) and mature granule cells (NeuN+). We show that GHSR was not expressed in Sox2+, Nestin+ or Ki67+ NSPCs in the DG. However, GHSR was highly expressed on mature DG NeuN+ cells.

Next, adult male rats were used to determine the effects of AG treatment on adult hippocampal neurogenesis (AHN). They were given daily i.p. injections of saline or AG (10µg/kg) for 2 weeks and on day's 5-8 BrdU (50mg/kg) was given to label dividing cells. On day 28 brains were collected for analysis of newly generated (BrdU+/NeuN+) neurones, rates of stem cell renewal (BrdU+/Sox2+/S100β-) and new astrocytes (BrdU+/Sox2+/S100β+). AG treatment significantly increased AHN (BrdU+/NeuN+, $P<0.001$) in the rDG. There was no significant effect on the rate of stem cell self-renewal or new astrocyte formation in the DG. Next, using a similar BrdU pulse-chase method, adult male and female GHSR KO mice and WT littermates were used to determine the effect of CR (70% calories of ad-lib fed group) on AHN. CR was shown to induce a 52% increase in rDG AHN (BrdU+/NeuN+, $P<0.05$) in a GHSR-dependant manner.

Lastly, we quantified circulating levels of AG in healthy humans (n=20) and in a cohort of patients diagnosed with Parkinson's disease dementia (n=8). AG was significantly reduced ($P<0.05$) in plasma from PDD patients.
In summary, these data suggest that AG may be a biomarker of dementia and that elevating circulating AG represents a novel therapeutic approach for preventing cognitive decline in humans.

Contact email address: 364437@swansea.ac.uk

Poster number: P-W079
Theme: Neurodegenerative disorders & ageing

Vulnerabilities to inflammatory exacerbation and acute cognitive dysfunction in a mouse model of Alzheimer's disease

Authors: Ana Belen Lopez-Rodriguez, Edel Hennessy, Carol Murray, Niamh de Barra, Colm Cunningham - *Biochemistry Trinity College Dublin*

Inflammation is believed to contribute to Alzheimer's Disease (AD), but mechanisms remain unclear. Microglia priming was first described in a prion disease model as an exacerbated response of microglia to subsequent central or systemic inflammatory challenges. The aim of this work was to define the primed signature in APP/PS1 mice based on our previous results and other more recent microarray studies in purified microglia; as well as to assess vulnerability to acute cognitive dysfunction upon acute inflammatory activation in this AD model. Initially, we administered intracerebral (i.c.) IL-1β or LPS to wild type (WT) or transgenic APP/PS1 (TG) animals (17±1 months) and examined the cytokine expression at 2h post-challenge by PCR and immunohistochemical techniques. Histologically, we found a robust Iba-1 positive microglial population surrounding amyloid plaques and these cells showed an exaggerated IL-1β production, in comparison with WT mice. We also assessed whether these exaggerated responses were apparent after i.p. LPS challenge. Quantitative PCR revealed an increase in C1q-α and CD68 in TG mice with respect to WT mice and both IL-1β and CD14 showed exaggerated expression upon systemic challenge with LPS. These data show that microglia are primed in APP/PS1 mice to produce exaggerated IL-1β responses to acute LPS challenge, whether centrally or systemically applied. Astrocytes also showed an increased reactivity at the histochemical and molecular level in TG mice in comparison with WT (GFAP expression); however, further analyses are currently being undertaken to establish if the astroglia are similarly primed. We then tested the acute behavioural and cognitive consequences of LPS (100 µg/kg i.p.). LPS induced a mild decrease in core-body temperature and in the number of squares in the open field without differences between both genotypes. However, in a Y-maze cognitive flexibility task, TG mice treated with LPS showed significantly increased incorrect trials per block; suggesting that, although both strains were equally sick, there is a selective vulnerability to cognitive dysfunction in TG animals upon systemic inflammatory challenge. The findings have implications for understanding the inflammatory vulnerability of the AD brain and delirium.

Contact email address: lopezroa@tcd.ie

Poster number: P-W080
Theme: Neurodegenerative disorders & ageing

Burden of genetic polymorphisms in the mTOR regulated pathways predict Alzheimer's disease risk

Authors: Brian Bempong, Jacob Bradbury, Dr Zsuzsanna Nagy - *Institute of Inflammation and Ageing University of Birmingham*

Previous work suggests that dysregulation of the mTOR pathway is associated with increased risk of Alzheimer's disease (AD).
It has been shown that genes involved in downstream signalling of mTOR are highly polymorphic in humans.
Recently, we have identified specific genes and SNPs associated with mTOR dysregulation.
The aim of this study was to examine whether the genetic variations associated with mTOR dysfunction are able to discriminate between Alzheimer patients and healthy controls or not.

Methods
Genetic data was collected from elderly cohorts of European descent, which included both Alzheimer patients and age matched healthy controls. Early onset Alzheimer's patients were excluded from the study.
Data analysis was performed using the Ingenuity Variant Analysis and Metaboanalyst software to determine the relationship between variation burden on mTOR regulated pathways and disease state.
ROC curve analysis was used to determine the accuracy of the diagnostic prediction using the pathway burden indicators.

Results
Statistical analysis of SNP data achieved significant discrimination between AD patients and healthy controls based solely on the effects of SNPs in the pathways downstream of mTOR.

Conclusions
Genetic array analyses of the effect of SNPs in mTOR associated pathways provides an accurate prediction of Alzheimer's disease risk in populations of European descent.
These findings support previous research linking dysfunction of the mTOR regulated pathways to AD susceptibility.

Contact email address: b.bempong@bham.ac.uk

Poster number: P-W081
Theme: Neurodegenerative disorders & ageing

Investigating longitudinal changes in brain function in a novel locus coeruleus tau seeding mouse model of Alzheimer's disease

Authors: Callum Walsh - *School of Physiology, Pharmacology and Neuroscience University of Bristol*, Abdellah Ahnaou - *Neuroscience Drug Discovery Janssen Pharmaceutica*

Background: Recent high profile failures of late stage Alzheimer's disease (AD) compounds have led many in the field to critically analyse the translatability of currently available AD mouse models, and focus on earlier disease interventions. We aimed to introduce a novel mouse model of Alzheimer's disease, utilising tau seeding to initiate tau pathology in the locus coeruleus (LC) of tau transgenic P301L mice, to better model the early stages of Alzheimer's disease. Using this novel model, we have investigated longitudinal changes brain function in key brain regions of these animals, as measured by EEG, to identify possible functional biomarkers that could be used to test the preclinical efficacy of tau-targeted compounds. Experimental Approach: Male P301L mice underwent unilateral stereotaxic injections of K18 aggregates or buffer into the LC and were fitted with 6 stainless steel recording electrodes in the frontal cortex and hippocampal CA1 and CA3 regions. Following recovery, these animals underwent weekly spontaneous EEG recording sessions for 20 weeks.

This data was analysed with power spectral, coherence and phase-amplitude coupling (PAC) analyses, for investigation into neural network function. Following this, these animal's brains were used for immunohistochemistry (IHC) to investigate the extent of tau pathology spread. Key Results: Tau seeding resulted in numerous alterations within the ipsilateral and contralateral hippocampus, notably: reduced spectral power within a range of frequency bands at the ipsilateral CA1; impaired theta-gamma PAC at the ipsilateral CA1, and deteriorating theta-gamma PAC at the contralateral CA1; and reduced gamma frequency coherence between ipsilateral and contralateral CA1 regions. IHC revealed an absence of tau pathology within the hippocampi of all animals. Conclusions: Tau seeding in the locus coeruleus resulted in numerous alterations in functional hippocampal network function, in the absence of tau pathology spread to these regions. Some of these alterations show promise as functional biomarkers, and these

results suggest that robust functional impairments in the hippocampus in the AD brain can be elicited by distant tau pathology relatively confined to the brainstem.

Contact email address: cw13178@my.bristol.ac.uk

Poster number: P-W082
Theme: Neurodegenerative disorders & ageing

Perceptual deficits in Parkinson's disease visual hallucinations revealed by hierarchical drift diffusion modelling

Authors: Claire O'Callaghan - *Psychiatry University of Cambridge*, Julie M Hall - *Brain and Mind Centre University of Sydney*, Alessandro Tomassini - *Cognition and Brain Sciences Unit University of Cambridge*, Alana J. Muller - *Brain and Mind Centre University of Sydney*, James M Shine - *Psychology Stanford University*, Simon JG Lewis - *Brain and Mind Centre University of Sydney*

A significant subset of Parkinson's disease (PD) patients develop visual hallucinations, however their exact causal mechanisms remain poorly understood and treatment options are limited. Previous work has suggested that deficits in attentional processing contribute to the emergence of hallucinations in PD. The current study aimed to characterise the cognitive mechanisms contributing to attentional deficits in PD hallucinators. In 50 patients with PD (24 hallucinators and 26 non-hallucinators) and 13 controls, we administered the Attentional Network Task (ANT) to compare processing of neutral, congruent and incongruent perceptual stimuli. We applied a Bayesian hierarchical drift diffusion model, which allowed us to determine the latent psychological processes underlying task performance, including: drift rate, decision boundary threshold, bias and non-decision time. Behavioural results revealed that both PD hallucinators and non-hallucinators had slower reaction times compared to controls, but response accuracies were equivalent. Model comparison and simulations were performed to identify a model with the best fit, which incorporated drift rate and decision boundary threshold for each condition, and non-decision time. Results revealed that PD hallucinators had significantly slower drift rates compared to non-hallucinators and controls, whereas decision thresholds and non-decision times were equivalent for hallucinators and non-hallucinators. Slow drift-rates in hallucinators are consistent with a slower, more error prone perceptual decision making process where evidence accumulation is more vulnerable to noisey information. These findings highlight a potential cognitive mechanism contributing to attentional deficits in PD hallucinations, suggesting that inefficient perceptual processing may contribute to the development of visual hallucinations.

Contact email address: co365@cam.ac.uk

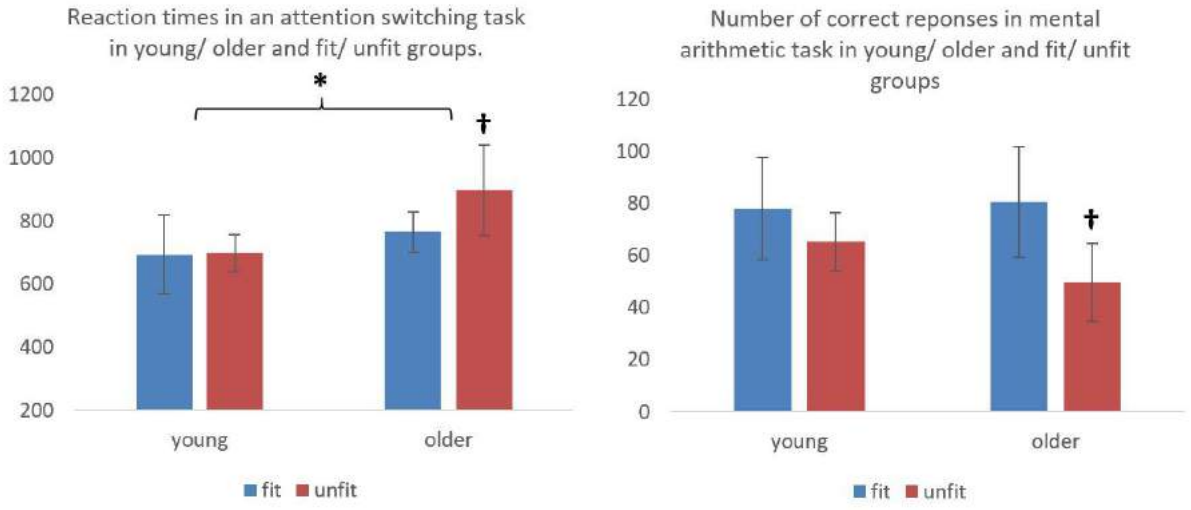
Poster number: P-W083
Theme: Neurodegenerative disorders & ageing

Aerobic fitness offsets age related decline in performance on attention switching and mental arithmetic tasks.

Authors: Claire V Burley, Anna C Whittaker - *School of Sport, Exercise & Rehabilitation Sciences University of Birmingham*, Karen Mullinger - *School of Psychology University of Nottingham*, Samuel JE Lucas - *School of Sport, Exercise & Rehabilitation Sciences University of Birmingham*

Performance on cognitive tasks that rely on the prefrontal cortex (e.g., attention switching task (AST) and mental arithmetic) naturally decline with age and are impaired in neurodegenerative disease (e.g., dementia). More recently, the effects of physical exercise interventions on such brain outcome measures have been investigated but report conflicting findings. This is possibly due to a lack of clarity around the underlying mechanisms targeted or consistency in the outcome measures assessed. PURPOSE: The aim of this cross sectional study was to investigate whether differences in cognitive performance will be observed between young and older individuals, with high or low fitness. METHODS: Thirty-one healthy volunteers in two age groups: young (20 – 40 yrs; mean age 25 ± 7 yrs; 9 fit, 9 unfit; VO2max >45 mL·kg·min-1 vs. <40 mL·kg·min-1) and older (60 – 80 yrs; 69 ± 5 yrs; 6 fit, 7 unfit; VO2max >30 mL·kg·min-1 vs. <20 mL·kg·min-1) participated. During separate visits they completed an aerobic fitness test (VO2max), cognitive tasks (5 tasks; CANTAB software) and a paced auditory serial addition task (PASAT). RESULTS: Between group ANOVAs revealed significant differences between all mean AST measures between young and older groups (all $p < .005$), such that the performance in the older groups was much slower than the younger groups. When comparing between fitness groups, no differences were observed with fitness in the young group (ranging from $p = .617$ to $p = .941$); however, in the older group there was a trend for a difference between fit and unfit individuals for most tasks (ranging from $p = .054$ to $p = .428$), and the older fit group performed significantly better for the ASTLDM (latency direction mean) measure ($p = .032$) (where participants were required to

respond to the direction of an arrow and ignore conflicting information given about the side). Further, in the PASAT, significant differences were observed in the older group between fit and unfit individuals on the number of correct responses given (p=.004). CONCLUSION: Performance in AST declines with age but there is some evidence that it is offset by physical fitness. Further, in older adults higher physical fitness is associated with higher correct responses in a mental arithmetic task.



* difference between age groups ($p < .05$); † difference between fitness groups ($p < .05$)

Contact email address: cvb469@bham.ac.uk

Poster number: P-W084
Theme: Neurodegenerative disorders & ageing

Ageing and progressive microgliosis imposes progressive vulnerability to acute cognitive dysfunction upon systemic inflammation

Authors: Dáire Healy, Carol Murray, Colm Cunningham - *School of Biochemistry Trinity College Dublin*

Compelling and growing evidence continues to define the crucial role that inflammation plays in the progression of neurodegenerative diseases and ageing. Microglia, the brain's primary resident macrophage population forms an integral part of our inflammatory response to systemic and central insults. However, under chronic activation, such as that imposed in neurodegenerative conditions, it has been shown that they adopt a "primed" phenotype characterised by an exaggerated inflammatory response to secondary insults. This phenotype has also been shown to be present in ageing and we hypothesized that microglial priming would increase with age leading to a progressive increase in vulnerability to cognitive dysfunction induced by systemic inflammation. To test this hypothesis, we conducted behavioural studies of mixed gender cohorts of normal C57BL6 mice at three ages (6, 17 & 24 months old) challenged intraperitoneally (i.p.) with LPS (100µg/kg) and Poly I:C (12mg/kg) to mimic bacterial and viral infections in vivo. Both LPS and poly I:C induced acute working memory dysfunction at 24m that was largely absent at 6 and 17m. With a focus on older animals (25m) we demonstrate exaggerated hypothermic and sickness behaviour responses to LPS (100 µg/kg i.p.) in 25m animals with respect to 8m. We predicted that an increased microglial activity was a key contributor to this exaggerated vulnerability in ageing. To begin to elucidate the molecular underpinnings of this we conducted quantitative PCR to assess markers of microglial activation and acute inflammatory mediator production. The data indicate a clear activation of the complement system (C1q-α, C3, cd11b) and type I interferon pathway as well as an exaggerated IL-1β response to acute LPS stimulation. Further analysis of regional differences of these microglial profiles is underway. These data suggest that microglial priming increases with age and contributes to a progressively increasing susceptibility to secondary inflammatory insults and have significant implications for both dementia and delirium.

Contact email address: healyd9@tcd.ie

Poster number: P-W085
Theme: Neurodegenerative disorders & ageing

Age-related differences in resting heart rate variability are associated with intrinsic functional brain connectivity but not with brain structure

Authors: Deniz Kumral, Frauke Beyer - *Neurology Max Planck Institute Human Brain and Cognitive Science*, Franz Liem - *Max Planck Research Group, Neuroanatomy & Connectivity Max Planck Institute Human Brain and Cognitive Science*, Daniela Husser - *Leipzig Research Center for Civilization Diseases, University of Leipzig,* Matthias L. Schroeter - *Neurology Max Planck Institute Human Brain and Cognitive Science*, Miray Erbey - *Berlin School of Mind and Brain Humboldt-Universität zu Berlin*, *Germany*, Janis Reinelt, Josefin Roebbig, H.Lina Schaare - *Neurology Max Planck Institute Human Brain and Cognitive Science*, Andrea Reiter - *Lifespan Developmental Neuroscience, Technical University of Dresden, Germany*, Markus Löffler - *Institut für Medizinische Informatik, Statistik und Epidemiologie University of Leipzig*, Arno Villringer, Michael Gaebler - *Neurology Max Planck Institute Human Brain and Cognitive Science*

Resting heart rate variability (HRV) indexes autonomic cardioregulation, is used as an individual trait marker, and has been related to physiological and psychological well-being (Thayer et al., Neurosci Biobehav Rev 2012). Studies have associated HRV with brain structure (e.g., Winkelmann et al., Brain Struct Func 2016) and function (e.g., Chang et al., NeuroImage 2013). Given that HRV is known to decrease with age, we hypothesized that neural correlates may also differ with aging. Thus, we investigated the relationship between resting HRV, brain structure and resting-state functional connectivity in adults of different age groups. We used two data sets: Sample 1 included 273 healthy subjects (young: 28±4y, middle: 47±6y, old: 67±5y) from a large epidemiological study (Löffler et al., BMC Pub Health 2015). Sample 2 was used for confirmatory analysis and consisted of 53 healthy young subjects (24±3y) from an independent dataset. To measure parasympathetic cardioregulation, we calculated the root mean square of successive differences (RMSSD in ms: see Malik et al., Ann Noninvasive Electrocardiol 1996) of interbeat intervals and related it to both structural (voxel-based morphometry; Ashburner & Friston, NeuroImage 2010) and functional (eigenvector centrality mapping; Lohmann et al., PLOS One 2010) 3T MRI data. We did not observe significant changes in grey matter volume associated with resting HRV. In sample 1, we found a progressive decline of HRV with age ($r = -0.45$, $p < 0.001$). Higher HRV was significantly associated with increased centrality in right posterior cingulate cortex in all age groups and in bilateral ventromedial prefrontal cortex (vmPFC) in young subjects only (significant age group by HRV interaction, see Figure). In sample 2, we confirmed the vmPFC finding in young subjects. These two regions are central components of the default-mode network (Beissner et al., J Neurosci 2013) and have previously been associated with fluctuations in HRV. Our finding that vmPFC is no longer related to HRV in the elderly supports the view that the well-known HRV decrease in aging may have a central neural component leading to attenuated parasympathetic cardioregulation.

Contact email address: dkumral@cbs.mpg.de

Poster number: P-W086
Theme: Neurodegenerative disorders & ageing

An EEG study examining how ageing influences false-belief reasoning abilities

Authors: Elisabeth E.F. Bradford, Victoria E.A. Brunsdon, Heather Ferguson - *School of Psychology University of Kent*
The ability to understand other people's mental states – beliefs, desires, knowledge – plays a key role in everyday life, allowing individuals to engage in successful interactions and to communicate successfully. It has previously been shown that social-cognitive abilities such as these can decline with age, even in healthy individuals. The research presented here assessed potential differences in the neural basis of social-cognition abilities across the lifespan, exploring whether differentiations in belief-processing continue across the lifespan, or whether differentiations are reduced as social-cognitive abilities decline with healthy ageing. EEG measures were taken whilst participants (aged 18 – 80+ years) listened to a series of short stories in which a character held a true or false belief about the location of an object. The character was then described as acting in a manner consistent or inconsistent with this belief-state (i.e. the location they looked in for an object). Analysis using event-related potentials demonstrated that for both younger and older adults, there was a significant difference in how true and false-belief states were processed, with a significant role of belief-consistent versus belief-inconsistent actions of the character. When the character was in possession of a false-belief, belief-consistent outcomes led to a more negative-going N400 component than belief-inconsistent outcomes. Whilst following similar patterns, these distinctions were more pronounced in the older adult group than the younger adult group. Results indicate potential differences in the processes underlying belief-state reasoning across the lifespan.

Contact email address: E.E.Bradford@kent.ac.uk

Poster number: P-W087
Theme: Neurodegenerative disorders & ageing

Interleukin-1 Receptor Antagonist (Il-1ra) and Brain Endocannabinoids Crosstalk to Control Neurogenesis

Authors: Francisco Molina-Holgado, Kelly Shevonne de Couteau, Volker Behrends, Laurent Lacroix - *Life Sciences University of Roehampton*

Crosstalk between neuroimmune networks and the brain endocannabinoid (eCB) system contribute to the maintenance of neurogenesis. Moreover, the eCB system directs cell fate specification of neural stem cells (NSC) in the central nervous system (CNS). We have previously shown that the activation of CB1 and CB2 cannabinoid receptors suppressed chronic inflammatory responses through the attenuation of pro-inflammatory mediators such as interleukin-1β (IL-1β) by increasing the expression of IL-1 receptor antagonist (IL-1RA), an endogenous antagonist for the actions of IL-1 in the CNS. Endogenous IL-1RA mediates the neuroprotective and anti-inflammatory actions of CBs in primary neurons and glia. These effects appear to be mediated by both CB1 and CB2 receptors. CB-induced IL-RA release may negatively regulate IL-1 actions in the brain, via IL-1RA blocking the IL-1 receptor (IL-1RI), after inflammatory or excitotoxic insults. Interestingly, receptors for cannabinoids (CB1 and CB2 receptors) and interleukin-1 are co-expressed in NSC. In order to further explore the effects of IL-1RA on endocannabinoid signalling in NSC the levels of the endocannabinoids 2-arachidonylglycerol (2-AG), 1-AG and anandamide (AEA) were detected using liquid chromatography-mass spectrometry (LC-MS) on a Waters Acquity H-Class UPLC coupled to TQSmicro triple quadrupole mass spectrometer following IL-1RA treatment. Treatment with IL-1RA caused marked increases in the levels of AEA (approximately three-fold) and 2-AG (approximately three-fold) in NSC nuclear extracts respectively, compared to the control group. Whereas, in supernatants the levels of 2-AG and 1-AG and AEA were similar to that obtained in the control group. In this study we show for the first time that acute administration with IL-1RA significantly increases levels of AEA and 2-AG in NSC. Thus it may be hypothesised that IL-1RA increases proliferation by increasing the levels of endocannabinoids, which acts via CB1 or CB2 receptors. These results provide crucial new insights into the effects of IL-1RA in regulating NSC proliferation and the pathways involved, and highlight the therapeutic potential of their interplay with eCB signalling in brain repair.

Contact email address: f.molina-holgado@roehampton.ac.uk

Poster number: P-W088
Theme: Neurodegenerative disorders & ageing

Developing Technology to Enable Macroscopic Imaging of Neuronal Connectivity to Quantify Changes During Health and Disease

Authors: Gerald Moore - *Life Sciences Imperial College London*, Yu Liu - *Bioengineering Imperial College London*, Diana Lucaci - *Life Sciences Imperial College London*, Simon Schultz - *Bioengineering Imperial College London*, Stephen Brickley - *Life Sciences Imperial College London*

Ageing population studies assessing semantic and episodic memory ability has revealed a decline in cognitive performance over the aging process. We suspect cognitive impairment results from changes in neuronal connectivity, but this theory is not fully established. Furthermore, how age dependent changes impact brain function and its influence on the manifestation and progression of disease, is yet to be intimately explored. We are therefore developing and utilizing novel technologies to investigate the connectomics of the brain, by combining serial two-photon tomography with neuronal tracing techniques. By inspecting neuronal circuits, we can establish age dependent changes, their effect on brain function, and their role in disease such as dementia. With the population of those aged 60 years or over is projected to increase by 60% over the next 15 years, understanding the impact of age and disease on brain function can lay the bedrock for ensuring the aged population maintain healthy and functioning lives. In this study, we demonstrate the feasibility of this technique with an investigation of Sox14 driven GFP expressions in the mouse brain. Quantitative analysis of Sox14 interneuron density across different thalamic nuclei was performed in order to map a novel 3D tomography data-set with a mouse brain atlas via a registration process; an important step when assessing changes in the ageing brain.

Contact email address: gm515@imperial.ac.uk

Poster number: P-W089
Theme: Neurodegenerative disorders & ageing

Genetic determinants of Rapamycin response in lymphocytes

Authors: Jacob Bradbury, Brian Bempong, Dr Zsuzsanna Nagy - *Institute of Inflammation of Ageing, University of Birmingham*

Previous work suggests that reduced rapamycin response in peripheral blood mononuclear cells (PBMC) is associated with an increased risk of Alzheimer's disease. We propose that this altered rapamycin response in PBMCs is due to genetic variations on the genes regulating mTOR dependent cellular functions.

Methods
Blood samples were taken from a cohort of age matched Alzheimer patients, healthy controls and patients with mild cognitive impairment. All subjects were of European descent.
Lymphocytes were separated from blood, and the Rapamycin response was tested using established protocols (Yates et al 2013).
Whole exome sequencing (WES) data was analysed using the Ingenuity Variant Analysis and Metaboanalyst software to determine the relationship between variation burden on mTOR regulated pathways and the actual Rapamycin response test result.

Results
The results indicate that the burden of genetic variations on the mTOR regulated pathways was a strong predictor of the Rapamycin response in PBMCs. The accuracy of the prediction was better when all SNPs (common and rare) were included in the analysis. Although the exclusion of rare (<1% MAF) variants reduced the AUC and increased the 95% confidence interval, the panel of common SNPs on mTOR regulated genes is sufficient to predict the Rapamycin response accurately.

Conclusions
Our study indicates that the Rapamycin response in PBMCs indeed is determined mostly by genetic variations of the genes downstream from mTOR.
We also find that it is sufficient to genotype the common SNPs on these genes to predict the Rapamycin response accurately.

Contact email address: J.S.bradbury@bham.ac.uk

Poster number: P-W090
Theme: Neurodegenerative disorders & ageing

Impact of MAPT (tau) haplotype with the pathology of Parkinson's disease

Authors: Lara Friess - *Nuffield Department of Clinical Neurosciences Oxford Parkinson's Disease Centre, Oxford, UK*, Ilaria Guella - *Department of Medical Genetics Centre for Applied Neurogenetics, University of British Columbia, Vancouver, Canada*, Daniela Petrova, Lefkos Middleton - *Neuroepidemiology and Ageing Research Unit School of Public Health, Imperial College London, UK*, Matthew Farrer - *Department of Medical Genetics Centre for Applied Neurogenetics, University of British Columbia, Vancouver, Canada*, Laura Parkkinen - *Nuffield Department of Clinical Neurosciences Oxford Parkinson's Disease Centre, Oxford, UK*
Genome wide association studies (GWAS) of Parkinson's disease (PD) have highlighted a previously unappreciated association between tau gene (MAPT) and PD. However, prior to GWAS, several genetic association studies had already shown a robust association between the MAPT H1 haplotype and increased risk of PD. We hypothesize that the PD patients with risk MAPT H1 haplotype may have an increased distribution and burden of cortical tau pathology which could contribute to the development of cognitive impairment in PD. In addition, we want to examine the potential effects of MAPT haplotype variation on the tau mRNA levels (3R/4R ratio) in the brain regions affected by PD-related pathology.

Using virtual microscopy digital imaging (Aperio Scanscope) and associated software we have developed algorithms that allowed the high-throughput quantitative analysis of both cortical alpha-synuclein (ASN) and tau pathologies in a large cohort of cases with Lewy body disorders (i.e. 130 PD, 76 PD with dementia, 75 dementia with Lewy bodies and 61 controls). Tau pathology has been quantified in the entorhinal cortex (EntCx), middle temporal gyri (MTG) and occipital cortex (OccCx) according to Braak's tau staging, whereas ASN pathology was quantified in EntCx/MTG as well as in parietal, frontal and cingulate cortices according to Braak's synuclein staging. Quantification includes both counts of ASN-immunopositive Lewy bodies and tau-immunopositive neurofibrillary tangles as well as load of neuritic component of both proteins that may have separate pathogenetic significance. All these patients have been sequenced on a custom designed high-throughput sequencing panel (SOLiD 5500xl platform), capturing the exonic regions of candidate genes previously associated to neurodegenerative disease (including MAPT). Data analysis between genetic, clinical and quantitative pathologic data is ongoing. In addition, we are examining MAPT mRNA expression using commercial Taqman assays in EntCx, striatum and OccCx in a smaller sub-cohort (~50 cases) with differential MAPT status. Understanding these regulatory effects and possible shifts in the equilibrium of aggregation/non-aggregation prone isoforms can be used as diagnostic or potentially predictive biomarkers of disease progression.

Contact email address: lara.frie@ndcn.ox.ac.uk

Poster number: P-W091

Theme: Neurodegenerative disorders & ageing

Age-dependent reduction in the network slow oscillation during sleep in mice

Authors: Laura E. McKillop, Simon P. Fisher, Nanyi Cui, Tomoko Yamagata - *Department of Physiology, Anatomy and Genetics University of Oxford*, Keith A. Wafford - *Erl Wood Manor, Windlesham Eli Lilly & Co. Ltd*, Vladyslav Vyazovskiy - *Department of Physiology, Anatomy and Genetics University of Oxford*

Cortical population activity during sleep is characterised by periods of generalised neuronal silence (OFF periods), which correspond to slow waves on the electroencephalogram (EEG) or the local field potential (LFP). Sleep undergoes changes with ageing, both with respect to sleep-wake architecture and cortical EEG. However, it is unknown whether local cortical network dynamics are also affected by age.

We performed chronic recordings of LFPs and multiunit activity (MUA) from the primary motor cortex of freely moving male C57BL/6J mice (early adulthood, EA: 5.06±0.07 months, n=6; old age, OA: 24.69±0.36 months, n=6-7), using 16-channel microwire arrays. We analysed undisturbed 12-hour baseline light periods followed by 6-hours sleep deprivation (SD) and recovery sleep the next day. The 16-channels of MUA were concatenated to obtain population activity. LFP power spectra were calculated for artifact free epochs of NREM sleep, and averaged between 0.5-4 Hz to obtain slow-wave activity (SWA, 0.5-4Hz). OFF periods were defined as total neuronal silence across all channels lasting >100ms.

After SD, initial levels of LFP SWA were significantly lower in OA mice as compared to EA (% baseline: EA: 190.51±11.37%; OA: 159.65±11.92%; p=0.005). This difference was attenuated when all LFP channels were averaged (% baseline: EA: 186.25±5.75%; OA: 165.54±15.50%; p=0.07). To investigate the relationship between LFP slow waves and underlying neuronal activity, all detected OFF periods were aligned to their onset and the corresponding LFP signals were averaged. OFF periods were associated with a positive LFP slow wave in both ages. However, the average amplitude of the slow-wave triggered by OFF-periods was substantially reduced in older animals as compared to young (EA: 164.19±43.94 µV; OA: 59.85±12.53 µV; p=0.02), despite similar average OFF period duration (EA: 135.28 ms; OA: 139.98 ms, ns).

Our preliminary results suggest that the spiking activity and silence of cortical neurons may be uncoupled from the slow LFP oscillation in older animals, as they had a reduced capacity to generate high amplitude slow waves in relation to population OFF periods. We therefore propose that ageing alters the balance between local and global cortical synchronisation during sleep.

Contact email address: laura.mckillop@dpag.ox.ac.uk

Poster number: P-W092
Theme: Neurodegenerative disorders & ageing

Mitochondrial composition of the Pipistrelle bat connects increased fatty acids and decreasing FABP3 with longevity.

Authors: Lisa Chakrabarti, Amelia Pollard - *SVMS University of Nottingham*, Amelia Pollard, Freya Shephard, Lisa Chakrabarti - School of Veterinary Medicine and Science, University of Nottingham, Sutton Bonington, UK, LE12 5RD, UK, Catharine A. Ortori, David A. Barrett - Centre for Analytical Bioscience, School of Pharmacy, University of Nottingham, NG7 2RD, UK, Susan Liddell - School of Biosciences, University of Nottingham, Sutton Bonington, UK, LE12 5RD, UK

The rate of living theory proposes smaller animals with higher metabolic rates have shorter lifespans. Mice have a maximum lifespan of 4 years, the recorded equivalent is 11 years in the Common Pipistrelle bat, which is exceptional. Mitochondrial dysfunction is associated with age-related decline in cognition and muscle strength. Proteins required for oxidative phosphorylation are differentially expressed in the bat and mouse mitochondria. We find high polyunsaturated fatty acids and N-acylethanolamines in the bat brain, these are considered neuroprotective, favouring mitochondrial functionality. In mouse skeletal muscle mitochondria, we found an increase in fatty acid binding protein 3 and a corresponding decrease in long chain fatty acids these are both associated with metabolic syndrome in ageing humans. Our comparison delineates metabolic profiles in the bat which are consistent with an intrinsic resistance to ageing processes.

Contact email address: lisa.chakrabarti@nottingham.ac.uk

Poster number: P-W093
Theme: Neurodegenerative disorders & ageing

Distribution of soluble Aβ in the brain after injection into cisternal CSF. Significance for Alzheimer's disease and intrathecal drug delivery.

Authors: Nazira Albargothy, James Booker, Roy O Weller - *Clinical and Experimental Sciences University of Southampton*, Ajay Verma - *Neurology, Drug Discovery and Development Center Biogen IDEC*, Cheryl A Hawkes - *Faculty of Science, Technology, Engineering & Mathematics The Open University*, Roxana O Carare - *Clinical and Experimental Sciences University of Southampton*
Acknowledgements: This work was supported by Biogen IDEC and Invicro.

Convective influx/glymphatic drainage of cerebrospinal fluid (CSF) into the brain parenchyma where interstitial fluid (ISF) resides has received much attention and the exact pathways of communication between CSF and ISF are not known. Here we test the hypothesis that soluble fluorescent amyloid-β (Aβ) injected into the cisterna magna of young mice enters along the glial-pial basement membranes of arteries, shows variation in depth of penetration into the brain tissue related to time after injection and the region of the brain examined. Adult mice were injected with 2 µL of 100 µM fluorescent Aβ1-40 into the cisterna magna. Three mice were sacrificed at 5 minutes after intracisternal injection and three mice were sacrificed 30 minutes after injection. Brains were processed for double-labelled immunofluorescence using antibodies against vascular smooth muscle actin and collagen. Sections from the level of the olfactory bulbs, cortex, ventricles, midbrain and cerebellum were analysed using a confocal SP8 microscope. Five minutes after intracisternal injection, Aβ was observed colocalized with collagen IV in the walls of leptomeningeal arteries and cortical arteries but not associated with veins or capillaries. 30 minutes after intracisternal injection, Aβ was observed in the walls of leptomeningeal and cortical arteries and veins. The distance that Aβ was observed within the parenchyma at 30 min after intracisternal injection was significantly higher compared to 5 min. In all mice, Aβ was observed in the walls of blood vessels within the brain and the farthest from the surface of the CNS within the parenchyma was the midbrain. Our results suggest that soluble tracers enter the parenchyma of the brain as early as 5 minutes after intracisternal injection along the arterial pial-glial basement membranes. This pathway is different from the pathway of drainage of Aβ from the parenchyma (significant for Alzheimer's disease), which occurs along the basement membranes surrounding smooth muscle cells. This study may have implications for intrathecal drug delivery.

Contact email address: na2c14@soton.ac.uk

Poster number: P-W094
Theme: Neurodegenerative disorders & ageing

Chronic exposure to low dose vanadium exacerbates the motor deficits in the Drosophila melanogaster PINK mutant model of Parkinson's disease

Authors: Samuel Ohiomokhare - *Department of Biosciences Durham University*, Amany Ladagu, ,James Olopade - *Environmental Toxicology and Neuroscience Unit University of Ibadan*, Ed Okello - *Department of Agriculture University of Newcastle*

Parkinson Disease (PD) is a progressive neurodegenerative movement disorder. The PD pathology is characterised by distinct types of cellular defects; abnormal protein aggregation, oxidative damage, mitochondria dysfunction and a selective loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc). The PD brain SNpc has also been found to have higher levels of iron than age-matched controls, which has been associated with mitochondria dysfunction. The cellular toxicity of the exogenous heavy metal, vanadium, has been recently shown to be exacerbated in the presence of iron in oligodendrocytes Progenitor Cells (OPCs). As a heavy metal nutraceutical, vanadium has also been used at low doses in different health supplement formulations. Environmental exposures to low dose vanadium can have deleterious effects on the population over extended periods. This study explored the interplay between vanadium with iron in an *in vitro* (Catecholaminergic a-differentiated (CAD) cells) and an *in vivo* model (PINK1 mutant *Drosophila melanogaster*). Exposure of differentiating CAD cells (for 6 days) to vanadium (sodium vanadate) resulted in significant neurotoxicity (>200 µM) which was ameliorated with an iron chelator, deferoxamine (DFO). In the *Drosophila melanogaster* model, a progressive decrease in the locomotor activity of the flies exposed to vanadium over time, was observed across the three groups tested: saline, L-dopa and vanadium (1 µM in liquid feed) treatment groups in the WT ($p<0.05$) and the Phosphatase and Tensin-induced Putative Kinase 1 (PINK 1) mutant flies ($p<0.05$). Notably, while exposure of PINK1 mutant fly to vanadium significantly exacerbated existing locomotor deficits ($P<0.05$), a slight improvement was observed with WT. Taken together, these findings provide new evidence for the potential differential effects of heavy metals in the healthy population and PD sufferers, which highlights the need for caution in using vanadium health supplements in individuals with neurodegenerative disease. Furthermore, these findings also offer a new therapeutic option for combatting the neurological effects of chronic exposure to vanadium accumulation in heavily polluted regions of the world.

Contact email address: s.o.ohiomokhare@durham.ac.uk

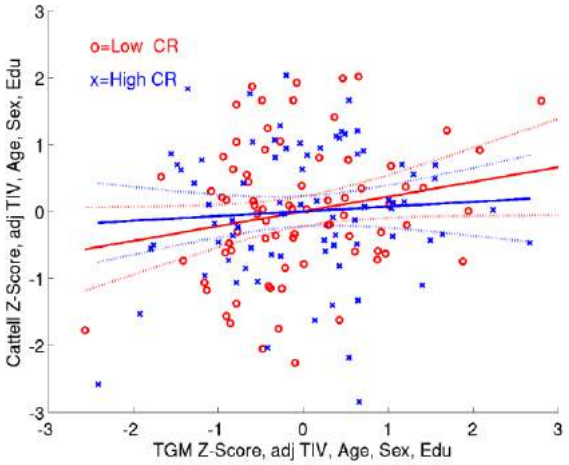
Poster number: P-W095
Theme: Neurodegenerative disorders & ageing

Modifiable contributors to cognitive reserve and their neural correlates

Authors: Richard Henson - *Cognition & Brain Sciences Unit Medical Research Council*, Lorraine Tyler - *Department of Psychology University of Cambridge*, Rogier Kievit, David Nesbitt - *Cognition & Brain Sciences Unit Medical Research Council*, Dennis Chan - *Clinical School University of Cambridge,Cam-CAN - University of Cambridge and MRC Cognition and Brain Sciences Cambridge Centre for Ageing and Neuroscience*, Meredith Shafto - *Department of Psychology University of Cambridge*

Cognitive Reserve (CR) is used to explain why some individuals maintain cognitive function despite declining brain health (BH) owing to aging and neurodegenerative disorders. Identification of modifiable contributors to CR would have major implications for public health strategies to prevent dementia. To test the hypothesis that activities in middle age contribute to CR , we analysed data from the Lifetime Experience Questionnaire (LEQ) from retired people aged > 55 in the Cambridge Centre of Ageing and Neuroscience (CamCAN; www.cam-can.org). The LEQ evaluates activities across three phases of adulthood (youth, middle age, old age), divided into activities “specific” to a phase (eg education vs occupation) and “nonspecific” activities (eg reading, sports and social activity). Cognition was assessed by the Cattell test of fluid intelligence. We found: 1) the degree of mental/physical activity in middle age made a unique contribution to Cognition in old age, and 2) this activity moderated the relationship between BH and Cognition.

In multiple regression with all 6 LEQ scores (N=162), plus sex and age, there was a significant, unique contribution to Cognition in old age from middle-age, non-specific activity (MNSA), T(153)=3.26, p=.0014 (R2=7%). The only other LEQ score making a significant contribution was youth specific activity (i.e, education), T(153)=3.27, p=.0013 (R2=7%). While the association of fluid intelligence with education is not surprising, the additional association with MNSA, over and above education, middle-age occupation and, most importantly, current mental and physical activities in old age, is noteworthy. Further evidence for MNSA contributing to CR would arise if the relationship between Cognition and BH were moderated by MNSA, such that Cognition in individuals with high CR were less dependent on BH. BH was measured by total gray matter (TGM), adjusted for total intracranial volume (TIV) (N=156). After a median split of MNSA, the correlation between BH and Cognition, after adjusting for age, sex and education, was significant in those with low CR (R=+.22, p=.05), but not in those with high CR (R=+.14, p=.23) (see Figure). This supports the hypothesis that middle-age activity protects cognition against brain atrophy in later years.



Contact email address: rik.henson@mrc-cbu.cam.ac.uk
Poster number: P-W096
Theme: Neurodegenerative disorders & ageing

An EEG study to investigate the human mirror neuron system and its relationship to social abilities in healthy ageing

Authors: Victoria E. A. Brunsdon, Elisabeth E. Bradford, Heather J. Ferguson - *School of Psychology University of Kent*

The human mirror neuron system may play an important role in social abilities, such as our ability to empathise and understand other people. The functioning of the human neuron system in healthy ageing and its relationship to social abilities has not been previously investigated. We therefore examined age-related differences in sensorimotor mu desynchronisation as an EEG marker of the human mirror neuron system across the pre-motor cortex, motor cortex and supplementary motor area during action

observation. Participants aged 18 to 86-years-old completed a hand movement observation task during EEG recording. Firstly, participants completed a 2-minute resting-state EEG as a reference period and, secondly, watched different video clips that depicted either a static hand or various hand actions, such as locking a door or clicking fingers. Participants also completed the Autism Quotient and Empathy Quotient as self-report measures of social abilities. For younger adults, we replicated previous findings of greater alpha and low beta desynchronisation during hand movement observation compared to static hand observation. We also found greater sensorimotor mu desynchronisation with increasing age. In addition, we examined how sensorimotor mu desynchronisation was related to general social abilities, including autistic traits and empathy ability. Therefore, this study reports the functioning of the human mirror neuron system across adulthood and how it may be related to social abilities.

Contact email address: v.e.a.brunsdon@kent.ac.uk

Poster number: P-W097
Theme: Neurodegenerative disorders & ageing

Alzheimer's disease and Mitochondria: Do mitochondrial alterations precede the onset of AD?

Authors: Victoria E. A. Brunsdon, Elisabeth E. Bradford, Heather J. Ferguson - *School of Psychology University of Kent*
The human mirror neuron system may play an important role in social abilities, such as our ability to empathise and understand other people. The functioning of the human neuron system in healthy ageing and its relationship to social abilities has not been previously investigated. We therefore examined age-related differences in sensorimotor mu desynchronisation as an EEG marker of the human mirror neuron system across the pre-motor cortex, motor cortex and supplementary motor area during action observation. Participants aged 18 to 86-years-old completed a hand movement observation task during EEG recording. Firstly, participants completed a 2-minute resting-state EEG as a reference period and, secondly, watched different video clips that depicted either a static hand or various hand actions, such as locking a door or clicking fingers. Participants also completed the Autism Quotient and Empathy Quotient as self-report measures of social abilities. For younger adults, we replicated previous findings of greater alpha and low beta desynchronisation during hand movement observation compared to static hand observation. We also found greater sensorimotor mu desynchronisation with increasing age. In addition, we examined how sensorimotor mu desynchronisation was related to general social abilities, including autistic traits and empathy ability. Therefore, this study reports the functioning of the human mirror neuron system across adulthood and how it may be related to social abilities.

Contact email address: wyin@lincoln.ac.uk

Poster number: P-W098
Theme: Neurodegenerative disorders & ageing

Characterization of hippocampal synaptic plasticity in a rat model of Alzheimer's disease amyloidosis

Authors: Yingjie Qi, Igor Klyubin, Micheal J Rowan - *Pharmacology and Therapeutics Trinity College Dublin*
Previously we reported that transgenic rats overexpressing mutant human APP (McGill-R-Thy1-APP) develop an Aß-dependent deficit in LTP induced by standard conditioning stimulation (200 Hz-HFS) as early as 3-4 months of age, whereas there was no deficit in LTP induced by a strong conditioning stimulation protocol (400 Hz-HFS) (Qi et al., Acta Neuropath. Comm., 2014). Here we studied the glutamate receptor-dependence of LTP induced by 400 Hz HFS and the ability of novelty exploration to reverse this LTP. Electrically evoked field EPSPs were recorded at CA3 to CA1 synapses in the dorsal hippocampus of chronically implanted adult freely behaving male rats. A cannula was also implanted in the lateral ventricle under recovery anaesthesia. In stratum radiatum LTP induced by 200 Hz-HFS, which is NMDA receptor-dependent, was completely inhibited in the transgenic rats. In contrast 400 Hz-HFS induced robust and large LTP both in wild type and transgenic littermates. Either CPP (an NMDA receptor antagonist) or mibefradil (a VDCC blocker) alone partly inhibited this 400 Hz-HFS-induced LTP. However, when both agents were given together, this robust LTP was totally blocked. We also examined the ability of novelty exploration to reverse previously established LTP, that had been induced by 400 Hz-HFS. Remarkably, behaviourally-induced LTP reversal (Qi et al., Cerebral Cortex, 2012) was strongly inhibited in the transgenic rats compared with wild type littermates. Different from LTP induced by 200 Hz-HFS at apical dendrites, LTP at basal dendrites in stratum oriens, induced by the same 200 Hz-HFS protocol, was not inhibited in transgenic rats at any age tested. In conclusion, although NMDA receptor-dependent LTP is inhibited in transgenic rats, an LTP that is both NMDA and VDCC-dependent is unaffected. Moreover, this robust form of LTP was resistant to reversal by novelty exploration in transgenic animals.

Contact email address: qiyi@tcd.ie

Poster number: P-W100
Theme: Learning & memory

A role for the nucleus accumbens in the hippocampal learning-behaviour translation?

Authors: Adam Seaton, Rebecca Hock - *Psychology University of Nottingham*, Charles Greenspon - *Life Sciences University of Nottingham*, Miriam Gwilt - *Psychology University of Nottingham*, Robert Mason - *Life Sciences University of Nottingham*, Tobias Bast - *Psychology University of Nottingha*

The role of the hippocampus in important types of rapid everyday learning, such as place learning, is well established. However, the mechanisms via which rapidly-acquired place memory may be translated into behaviour are yet to be determined. The intermediate hippocampus, which has been shown to be critical for the hippocampal learning-behaviour translation, combines neural substrates of accurate place encoding with links to prefrontal and subcortical behavioural control sites. This supports that these sites, including the nucleus accumbens (NAc), may be critical for this translation (Bast et al., 2009, PLoS Biol; Bast, 2011, Curr Opin Neurobiol). The NAc is a main candidate due to strong hippocampo-NAc projections that have been implicated in behaviour based on place memory (van der Meer et al., 2014, In: Space, Time and Memory in the Hippocampal Formation, ed. Derdikman & Knierim).

To examine the role of the NAc in the hippocampal learning-behaviour translation, we combined functional inhibition of the NAc (via microinfusion of the GABA agonist muscimol) with measurements of behavioural performance based on hippocampus-dependent rapid place learning using the watermaze delayed-matching-to-place test (DMTP) (Bast et al., 2009). In preparation for these studies, we conducted in vivo electrophysiological and sensorimotor experiments (locomotor activity, LMA and startle response/prepulse inhibition, PPI) to establish suitable muscimol doses to reduce NAc neuronal activity without causing gross sensorimotor side effects. Muscimol infusions into the NAc (125-250 ng/0.5 µl/side) reduced neuronal firing in the infusion site vicinity by 40-50% and, if at all, only moderately reduced LMA and PPI; the latter is consistent with findings that these sensorimotor functions mainly depend on the NAc core (Pothuizen et al., 2005, Neuropsychopharmacology), whereas our infusions targeted the NAc shell, which is the main recipient of hippocampo-NAc projections (Humphreys & Preston, 2010, Prog Neurobiol). Preliminary findings from our studies combining functional inhibition of the NAc with DMTP testing support that the NAc is required for performance based on hippocampus-dependent rapid place learning. Additional experiments to confirm and extend these findings are on the way.

Contact email address: stxaws@nottingham.ac.uk

Poster number: P-W101
Theme: Learning & memory

Opposing effects of reward and punishment during skill learning

Authors: Adam Steel - *FMRIB University of Oxford*, Edward H Silson - *NIMH National Institutes of Health*, Charlotte J Stagg - *FMRIB University of Oxford*, Chris I Baker - *NIMH National Institutes of Health*

The impact of reward (REW) and punishment (PUN), referred to here as feedback, (FB) on skill learning is not well understood. 72 participants (HVs) underwent fMRI during serial reaction time task (SRTT) or force tracking task (FTT) learning and received monetary REW, PUN, or control FB (CONT) based on their performance. For both tasks, stimuli followed a fixed sequence (SEQ) and skill was indexed early and late in training by comparing performance in SEQ and random (RAND) blocks. HVs in the SRTT (n=36) pressed buttons according to visually presented cues. HVs in the FTT (n=36) modulated their grip to match a target. SEQ and RAND BOLD responses were compared across the FB groups using an ANOVA with Group (CONT/REW/PUN), Type (SEQ/RAND), Epoch (Early/Late) as factors. In the SRTT, both REW and PUN showed more early skill than CONT (Group x Probe x Type: $F(2,33)=5.37$, $p<0.01$; PUN v CONT: $t(22)=3.46$, $p<0.005$, REW v CONT: $t(22)=2.55$, $p<0.02$). FMRI from the SRTT revealed a Group x Block Type interaction in bilateral cerebellum (biCereb), left ventral medial prefrontal cortex (lvmPFC), and right dorsal premotor cortex (rPMd). In REW, biCereb and rPMd activity was greater during SEQ compared to RAND blocks. PUN showed the opposite, reflecting the amount of FB given. During RAND blocks compared with SEQ blocks, lvmPFC activity increased in PUN and decreased in REW, reflecting FB valence. CONT showed no effect of Block Type. All groups showed skill in the FTT, but PUN improved less than REW (Main effect of Probe: PUN v REW: $t(35)=2.37$, $p<0.03$). FMRI data showed a Group x Epoch interaction in right middle temporal gyrus (rMTG), right caudate (rCaud), left superior parietal lobule (lSPL), and left cerebellum (lCereb). In REW, activity increased over time in all regions. In contrast, in CONT activity decreased in all regions. PUN was more complex: in rMTG activity increased over time, but in lSPL activity decreased over time. Pun did not impact rCaud or lCereb activity. In sum, in the SRTT, activity elicited by REW and PUN reflects FB frequency, and thus information, quickening learning. During FTT, REW causing activity to increase over time, which might reflect continued processing. Therefore, FB modulates regions responsible for skill learning, which impacts learning.

Contact email address: adam.steel@lincoln.ox.ac.uk

Poster number: P-W102
Theme: Learning & memory

Detecting neuronal assemblies using patterns of cross-correlations

Authors: Alexander Morley, Dr. David Dupret - *MRC BNDU University of Oxford*
The coordinated activity of subsets of neurons across multiple circuits is thought to support complex behaviours. These functionally coupled subsets are often referred to as cell assemblies. The detection of cell assembly patterns from single-unit recordings usually relies on finding significant co-firing within a particular time bin. Choosing a bin length based on synaptic integration times, e.g. 20 ms, makes these methods well-suited to detecting Hebbian-like cell assemblies within a single structure such as the hippocampus. However, for assemblies that span multiple circuits it may be that the assembly-forming neurons interact at longer latencies or over successive temporal windows. Here we apply independent component analysis to the cross-correlation between each neuron pair at multiple lags in order to incorporate these interactions. We show that this method is able to capture cross-structural assemblies, and contrast its performance to other methods, using both spike-train simulations and in vivo recordings from the rodent hippocampus and ventral tegmental area. Importantly we found that different assemblies detected in this manner show distinct neurophysiological correlates such as their coupling to different phases of hippocampal theta oscillations, responses during sharp-wave ripples, and speed modulation.

Contact email address: alexander.morley@univ.ox.ac.uk

Poster number: P-W103
Theme: Learning & memory

Neurochemical correlates of scene processing in the posterior cingulate cortex: a combined fMRI and 1H-MRS study

Authors: Alison Costigan - *CUBRIC, School of Psychology Cardiff University*

The posterior cingulate cortex (PCC)/precuneus is a core region of the default mode network (DMN) and may form part of an extended hippocampal-navigation system. This system is critical for performing complex scene discriminations, underpinning a broader role in episodic memory via re-experiencing spatial context. Functional magnetic resonance imaging (fMRI) studies have identified individual differences in the response of the PCC/precuneus specifically during scene processing, which may place people at increased risk of developing memory problems in later life. The neurochemical underpinnings of such scene processing activity differences are unknown.

Here, we combined 3T fMRI with proton magnetic resonance spectroscopy (1H-MRS) to explore how inter-individual variation in PCC BOLD-fMRI activity is related to the concentration of local metabolites. Participants (n=40, mean age 22 years) completed a perceptual odd-one-out fMRI task for scenes, objects, and faces. The metabolites N-acetyl-aspartate (tNAA), glutamate (Glx) and γ-amino-butyric acid (GABA+) were quantified via PRESS and MEGA-PRESS scans in PCC (2x2x3cm) and an occipital control voxel (3x3x3cm). TNAA is considered a marker of neuronal density and mitochondrial energy metabolism, and Glx and GABA+ indicate excitatory and inhibitory tone.

We found a category-sensitive PCC BOLD-tNAA relationship, such that the PCC BOLD response for scenes, but not faces and objects, was positively correlated with PCC tNAA. There was no significant correlation between PCC BOLD for scenes and occipital tNAA, suggesting regional selectivity of this relationship to the PCC. A complementary voxel-wise analysis within the PCC MRS voxel mask supported this finding, as this identified a significant cluster reflecting a positive association between scene-sensitive BOLD and PCC tNAA. There were no category sensitive relationships between PCC activity and PCC GABA+ or Glx.

These results demonstrate, for the first time, that variability in PCC BOLD during scene processing is related to PCC tNAA. This has implications for understanding individual differences in PCC/precuneus activity, and potential biochemical mechanisms that could underpin activity alterations in this region in disorders, for example Alzheimer's disease.

Contact email address: costiganag@cardiff.ac.uk

Poster number: P-W104
Theme: Learning & memory

Brain-derived neurotrophic factor and exercise-induced reversal of cognitive deficits in schizophrenia in the sub-chronic phencyclidine rat model

Authors: Antonio J Gonzalez, Lisa M Heaney, Giovanni Podda, Joanna M Oladipo, Ben Grayson, Michael K Harte, Charles Large, Joanna C Neill - *School of Pharmacy and Optometry University of Manchester*

Introduction: Cognitive deficits in schizophrenia remain an unmet clinical need and have a significant impact on outcome and quality of life for patients and carers (Harvey & Keefe, 2001). The sub-chronic phencyclidine (PCP) rat model and novel object recognition task (NOR) have been well validated for relevance to schizophrenia (Neill et al., 2010; Horiguchi et al., 2012; Grayson et al., 2015). Exercise increases hippocampal and plasma levels of brain-derived neurotrophic factor (BDNF), a protein that modulates synaptic change and long-term potentiation (Berchtold et al., 2005), providing a hypothesis for its beneficial effects in the illness. Our aim is to investigate the mechanisms of exercise-induced reversal of cognitive deficits in the scPCP model, with a focus on BDNF.

Methods: Four groups of adult female Lister Hooded rats (n=10 per group) were used: vehicle control, vehicle exercise, scPCP control, and scPCP exercise. Rats were treated with either saline or PCP (2mg/kg i.p.) twice a day for 7 days, followed by 7 days washout then given access to running wheels in individual cages for 1 hour a day, 5 times a week, for 6 weeks. Control groups had access to immobilised running wheels. Blood sampling and NOR (with a 1 minute inter-trial interval) were conducted pre- and post-exercise, and 2 weeks following exercise cessation. Plasma and hippocampal BDNF levels were quantified by ELISA. Data were analysed by ANOVA and post-hoc student's t-test.

Results: Pre-exercise vehicle, but not scPCP groups, successfully discriminated the novel from familiar object ($p<0.05$). The exercise regime reversed this cognitive deficit ($p<0.05$), while the scPCP control group remained unable to complete the task and vehicle groups successfully discriminated the novel from familiar object ($p<0.05$). The cognitive deficit reversal was sustained 2 weeks post-exercise ($p<0.05$). Current work is evaluating plasma BDNF and subsequent studies will measure brain BDNF in hippocampus and prefrontal cortex.

Conclusions: This work demonstrates that aerobic exercise reverses a robust cognitive deficit in a rat model for cognitive deficits in schizophrenia. Our work to evaluate potential mechanisms of this effect through BDNF could inform future therapeutic strategies in patients.

Contact email address: antoniojgonzalez195@gmail.com

Poster number: P-W105
Theme: Learning & memory

Object representation along the proximo-distal axis of CA1

Authors: Brianna Vandrey, James A. Ainge - *School of Psychology & Neuroscience University of St Andrews*

Models of episodic memory in the medial temporal lobe often suggest that spatial and non-spatial information reaches the hippocampus via the medial entorhinal cortex (MEC) and lateral entorhinal cortex (LEC), respectively. However, there is evidence that the LEC binds these two types of information together prior to the hippocampus. Further, the LEC contains neurons which are spatially tuned to objects. Notably, object-related firing in the LEC strongly resembles object-modulation of place cells in the hippocampus; neurons in both structures encode object location, respond to object displacement, and fire at locations where an object was previously located. However, the origin of object-modulation in place cells is unknown. One possibility is that input from the LEC drives the spatial representation of objects in the hippocampus. To explore this hypothesis, we implanted microdrives in rats (n=5), with tetrodes targeting either the proximal or distal CA1. These regions receive differential input from the entorhinal cortex, this strategy permitted us to record from neuronal ensembles which primarily receive MEC or LEC input. Place cells were recorded during exploration in an open-field containing objects which underwent a series of spatial manipulations, including object dislocation and novel object-place recognition. Object-modulated and non-object modulated place cells were recorded in both regions. Object-modulation of place cells in CA1 conformed to patterns which have been described previously. A sub-set of cells displayed 'trace' firing at previous object locations in response to the movement of objects within the environment. Place cells which receive LEC input contained more spatial information than those in which receive MEC input. Further, place cells which receive LEC input had increased stability across standard sessions where the objects underwent no change. These findings influence

our understanding of how entorhinal-hippocampal communication supports the integration of item and location information in episodic memory.

Contact email address: bmv@st-andrews.ac.uk

Poster number: P-W106
Theme: Learning & memory

Facilitation of Hebbian synaptic plasticity by convergent metabotropic and cholinergic signaling pathways.

Authors: Cezar M. Tigaret, Michael C. Ashby, Jack Mellor - *School or Physiology, Pharmacology and Neuroscience University of Bristol*

Induction of spike timing-dependent long-term potentiation (STD-LTP) at hippocampal Schaffer collateral (S/C)-CA1 synapses requires the sequential activation of postsynaptic NMDA receptors (NMDARs) and voltage-sensitive Ca2+ channels at dendritic spines (1, 2). Both NMDAR function and spine Ca2+ signals (EPSCaTs) during STD-LTP induction are facilitated by metabotropic glutamate receptor (mGluR1)-dependent inhibition of postsynaptic SK channels (2). In addition, muscarinic M1 receptors facilitate spine Ca2+ signals and induction of theta burst LTP at S/C-CA1 also via SK channel inhibition (3, 4). We now show in acute hippocampal slices from adult rats that the highly selective allosteric M1 agonist GSK-5 (5) (1µM) or the direct inhibition of SK channels by apamin (100 nM) rescued STD-LTP induction at S/C-CA1 synapses in the presence of mGluR1 selective antagonist YM 298198 (100 nM). Whole-cell current clamp recordings were performed at 36°C under GABAA receptor inhibition (50 µM picrotoxin). STD-LTP was induced with a theta frequency conditioning train of 300 spike pairings at 5 Hz for 1 min. Each pairing delivered one EPSP evoked in stratum radiatum followed by two post-synaptic action potentials elicited by somatic current injection, at 100 Hz. Two-photon Ca2+ fluorescence imaging in CA1 pyramidal cell dendritic spines showed that apamin enhanced synaptically evoked EPSPs and EPSCaTs. Furthermore, Ca2+ imaging during conditoning revealed that LTP induction requires a sustained sequence of spine EPSCaTs, which was facilitated by apamin. mGluR1 blockade inhibited the EPSCaTs during conditioning, and this effect was reversed in the presence of GSK-5. Our data indicate that SK channels are a common downstream target in a convergent signalling pathway for LTP facilitation by metabotropic glutamate and cholinergic neuromodulation.

1. Magee, J. C., and D. Johnston. 1997. Science 275:209-213
2. Tigaret, C. M., et al. 2016. Nat Commun 7:10289.
3. Giessel, A. J., & B. L. Sabatini. 2010. Neuron 68:936-947.
4. Buchanan, K. A., et al. 2010. Neuron 68:948-963.
5. Dennis S. H., , et al., 2016. Cereb Cortex 26:414-426.

Contact email address: TigaretC@cardiff.ac.uk

Poster number: P-W107
Theme: Learning & memory

Inter-regional theta phase synchronisation mediates human associative memory

Authors: Danying Wang, Andrew Clouter, Qiaoyu (Chloe) Chen, Kim L. Shapiro, Simon Hanslmayr - *School of Psychology University of Birmingham*

Hippocampal theta is thought to be crucial for binding sensory information from multiple cortical regions into coherent memory episodes. Studies in rodents showed that cortical inputs arriving at the appropriate hippocampal theta phase induce long-term potentiation, which is a possible mechanism for how theta phase modulates memory formation. Using a multisensory entrainment paradigm, we recently showed in humans that episodic memory performance is enhanced by theta (4 Hz) phase synchrony between visual and auditory cortices. In this current EEG study, we investigate if such theta phase synchrony between visual and auditory brain regions varies as a function of successful episodic memory formation. Scalp EEG activity is recorded while 24 healthy adults perform associative memory encoding and recall tasks. A series of sound-movie pairs are presented at encoding. Luminance of the movies and amplitude of the sounds are modulated from zero to full at 4 Hz with either 0 degree, in-phase or 180 degrees, out-of-phase to create phase offset in the visual or auditory cortices, respectively. Participants are asked to judge how well a sound corresponds to a movie while memorising the association between them. During later recall task, participants recall the correct scene presented with a given sound clip. Our preliminary results (N = 10) showed that 7 out of 10 participants had higher accuracy for the associative memory task in the in-phase condition than the out-of-phase condition, replicating our previous finding. Phase differences of the theta activity in 4 Hz between the auditory source and the visual source is categorised depending on later

associative memory performance. In the in-phase condition, subsequently remembered trials are predicted to be perfectly synchronised in phase with mean difference of 0. Phase differences of subsequently forgotten trials are predicted to have a more uniform distribution. In the out-of-phase condition, the pattern of remembered trials is predicted to resemble the pattern in the in-phase condition while the distribution of phase differences for the missed trials is predicted to be non-uniformed with a mean phase difference of 180. The findings will further our understanding of theta phase synchrony for episodic memory encoding.

Contact email address: D.Wang@bham.ac.uk

Poster number: P-W108
Theme: Learning & memory

Dopaminergic modulation of the neuronal networks underlying working memory

Authors: Emilie Werlen - *Experimental psychology University of Oxford*, Matthew W Jones - *Physiology, Pharmacology and Neuroscience University of Bristol*

Working memory relies on the prefrontal cortex (PFC) and is strongly modulated by dopaminergic signalling. However, the relationships between encoding of task-relevant information and responsivity of PFC neural subpopulations to dopaminergic input remain poorly defined. We therefore compared the behavioural correlates of rat medial PFC (mPFC) neurons during an instrumental delayed non-match to position (DNMTP) task with their responses to stimulation of dopaminergic projections from the ventral tegmental area (VTA).

Channel rhodopsin 2 was selectively expressed in tyrosine hydroxylase (TH)-positive neurons in the VTA of adult TH-Cre rats (n=3) simultaneously implanted with tetrode recording electrodes in hippocampal CA1 and mPFC. VTA stimulation (5ms pulses, 20Hz, 20mW) during wakefulness enhanced the power of low frequency oscillations in mPFC local field potential; 40% of 140 mPFC neurons responded to the same stimulation with significant increases or decreases in firing rate ($p<0.05$ by comparison with shuffled data). The responses of PFC neurons to VTA stimulation were not associated with their putative neuronal class (inferred from extracellular action potential waveforms and bursting characteristics), but were related to their behavioural correlates in the DNMTP task: neurons responding during the cue encoding phase of the task (sample lever press), or during reward consumption, were also significantly more likely to respond VTA photo-stimulation ($p<0.05$ vs. other classes of neuron).

These results indicate that mPFC principal neurons recruited to encode sample and reward information during a working memory task are more directly responsive than their peers to dopaminergic input from the VTA. These subpopulations may therefore preferentially contribute to dopamine's stabilisation of information in working memory.

Contact email address: emilie.werlen@psy.ox.ac.uk

Poster number: P-W109
Theme: Learning & memory

Limbic zif268 expression engaged by reactivation of a rewarded T-maze task memory is not required for stable performance

Authors: Emma Cahill, George H. Vousden - *Dept. of Psychology University of Cambridge*, Marc T.J Exton-McGuinness - *School of Psychology University of Birmingham*, Ian R.C Beh, Casey B. Swerner, Matej Macak, Sameera Abas, Cameron C. Cole, Brain F. Kelleher, Barry J. Everitt, Amy L. Milton - *Psychology University of Cambridge*

Pavlovian memories undergo reconsolidation, whereby the memory becomes unstable at reactivation and can be disrupted by amnestic agents. However, less is known about the reconsolidation of instrumental memories, whether these are goal directed (action-outcome) or habitual (stimulus-response). Our previous, preliminary data indicated that expression of a habit-like memory on a T-maze task correlated with an increase in Zif268, a protein critical for memory reconsolidation, in the posterior dorsolateral striatum. Here, the requirement for Zif268 for the restabilisation of a habit-like memory was tested by administering zif268 antisense oligodeoxynucleotides prior to memory reactivation; however, knockdown of Zif268 did not affect subsequent memory expression tested 24h, 7d and 28d later. Furthermore, when animals were more extensively trained, there was no correlation between the expression of the habit-like memory and Zif268 expression in the dorsal striatum, hippocampus, or nucleus accumbens. Zif268 expression increased in the basolateral amygdala after extended training, but this was not correlated with the use of a habit-like or goal-directed strategy during reactivation. We propose that Zif268 expression in the basolateral amygdala may

be linked to prediction error, generated by the absence of reward at re-exposure. Altogether this work supports the role of Zif268 in the maintenance of instrumental memories.

Contact email address: enc22@cam.ac.uk

Poster number: P-W110
Theme: Learning & memory

Projections from the nucleus reuniens to the CA1 region of the hippocampus are required for the formation of associative recognition memory.

Authors: Gareth Barker, Prof. E.C.Warburton - *Physiology, Pharmacology & Neuroscience University of Bristol*

Associative recognition memory, the ability to associate an object with a location or position in a sequence requires a neural network (Barker & Warburton 11). A recent study has identified a separation in the function of projections from the CA1 region of the hippocampus (HPC) to the medial prefrontal cortex (mPFC), thus deactivation of direct projections from the dorsal CA1 (dCA1) selectively impaired object-in-place memory whereas deactivation of direct projections from the intermediate CA1 (iCA1) selectively impaired temporal order memory (Barker et al 17). The nucleus reuniens of the thalamus (NRe) is one indirect route through which the mPFC can send information to the HPC and ablation of the nucleus reuniens impaired associative recognition memory formation (Barker & Warburton 15). Therefore this study aimed to test the hypothesis that projections from the NRe to the CA1 region of the HPC would show the same functional/anatomical dissociation between the dCA1 and iCA1 as was observed for the CA1 to mPFC projection.

Male Lister hooded rats were injected with a virus expressing an inhibitory DREADD (AAV5-hsyn-hM4Di) into the nucleus reuniens and cannula were implanted into the hippocampus targeting the dorsal (dCA1) and intermediate (iCA1) regions of the CA1. Different types of associative recognition memory were tested using spontaneous tests of preferential exploration. CNO (3µM) was infused either before the sample phase or before the test phase. A 4-way within subject design was used thus animals received either CNO infusion into either the dCA1, iCA1 or both or vehicle infusion into both dCA1 & iCA1.

In an object-in-place and an object temporal order task, infusion of CNO into the HPC before the sample phase resulted in impaired performance only when CNO was infused into both the dCA1 and iCA1, in contrast when CNO was infused before the test phase; in the object-in-place task performance was impaired after infusion into the iCA1 whereas in the object temporal order task performance was impaired after infusion into the dCA1. Thus the projection from the NRe to the HPC regulates associative recognition memory formation in distinct anatomical regions of the HPC dependent on the stage of memory processing and the type of association formed.

Contact email address: g.r.i.barker@bristol.ac.uk

Poster number: P-W111
Theme: Learning & memory

Classifying interneurons of the dorsal CA1 hippocampus from extracellular recordings

Authors: Gido van de Ven, Vítor Lopes-dos-Santos, David Dupret - *Department of Pharmacology MRC Brain Network Dynamics Unit, University of Oxford*

A variety of interneuron types has been identified in the rodent hippocampus based on differences in their post-synaptic targets, their expression of molecular markers and their spike timing relative to rhythmic fluctuations of the local field potential. Such interneuron types are thought to have distinct contributions to the temporal organization of principal cell firing. However, current progress in testing the role of each interneuron type has been hindered by the difficulty to assign interneurons to anatomically well-defined types when solely recorded with extracellular recordings (i.e., without further labelling) in behaving rodents.

Here we present results from a data set of 679 putative interneurons recorded using multichannel extracellular techniques from the dorsal CA1 region of the hippocampus of 38 mice. We employ an unsupervised clustering framework to attempt sorting interneurons into distinct types based on their (1) spike train dynamics, (2) spike waveform, (3) spatial tuning of their spike discharge, (4) spike coupling to well-known hippocampal oscillations, (5) coupling to the summed population activity of principal cells and (6) firing response to sharp wave-ripple oscillatory events.

Although we do not find clear support for the possibility to identify discrete types of interneurons solely based on their extracellular recordings, we do find structure in this dataset indicative of clusters of interneurons with overlapping firing properties. We suggest that our framework for an unsupervised interneuron clustering, although not absolute, nevertheless provides a useful way of classifying hippocampal interneurons that could contribute to further our understanding of their diverse roles in network dynamics and behaviour.

Contact email address: gido.vandeven@pharm.ox.ac.uk

Poster number: P-W112
Theme: Learning & memory

Synaptic transmission and plasticity require AMPA receptor anchoring via its N-terminal domain

Authors: Jake Watson, Hinze Ho, Ingo Greger - *Neurobiology MRC-LMB*

AMPA-type glutamate receptors are embedded at postsynaptic sites, aligned with the presynaptic neurotransmitter release machinery, mediating fast excitatory neurotransmission. As AMPARs diffuse rapidly in the plane of the membrane, a prerequisite for faithful signal transmission is their trapping and clustering at postsynaptic sites. Synapse strengthening, as occurs during learning, results from the recruitment to and enrichment of AMPARs at synapses. Therefore, the mechanisms underlying AMPAR positioning are fundamental to synaptic transmission and plasticity.

AMPAR synaptic anchoring has historically been explained by interactions of the receptor C-termini with components of the postsynaptic scaffold, yet this model has recently been challenged. Using mouse organotypic hippocampal slices, we show that the AMPAR N-terminal domain (NTD), which projects midway into the synaptic cleft, plays a fundamental role in this process. This highly sequence-diverse domain mediates synaptic anchoring in a subunit-selective manner. Using a combination of electrophysiological and imaging techniques we have revealed that receptors lacking the NTD exhibit increased mobility in synapses and are unable to maintain faithful synaptic transmission. Furthermore, despite being robustly expressed at extra-synaptic sites, AMPARs are unable to sustain long-term potentiation (LTP) without their NTD. Thus, synaptic transmission and plasticity are critically dependent upon an AMPAR anchoring mechanism that is driven by NTD interactions.

Contact email address: jwatson@mrc-lmb.cam.ac.uk

Poster number: P-W113
Theme: Learning & memory

Synchronization of cortical dendritic activity during sleep spindles in rodents

Authors: Julie Seibt - *Biochemical Sciences University of Surrey*, Clement J. Richard - *NeuroCure Charité - Universitätsmedizin Berlin,* Johanna Sigl-Glöckner - *BCCN Humboldt University of Berlin*, Naoya Takahashi - *NeuroCure Charité - Universitätsmedizin Berlin*, Denis de Limoges - *Insitute of Physiology University of Bern*, Christina Bocklisch - *NeuroCure Charité - Universitätsmedizin Berlin*, Matthew E. Larkum - *NeuroCure Humboldt Universität zu Berlin*

Sleep has now been linked to brain plasticity at many levels, with converging evidences from the molecular, cellular and behavioural fields. Studies in humans and animals support of specific role for spindle oscillations (9-16Hz) in this process but the underlying physiology remain elusive. It has been suggested that spindle bursts promote calcium increase specifically in dendrites, a condition that would favour dendritic plasticity processes (1, 2). Although this hypothesis is supported by computational modelling (1), to date, evidence that such a relation exists during natural sleep is missing.

To address this issue, we measured calcium activity from layer 5 (L5) dendrites in the somato-sensory cortex using one-photon (fibre-optic) and two-photon imaging in naturally sleeping rodents. Calcium imaging was combined with electroencephalographic (EEG) recordings to monitor behavioural states and underlying network oscillations.

Our results show that activity of population of dendrites during slow-wave-sleep was specifically correlated with spindle-beta (9-30 Hz) power changes. Two-photon imaging of single dendrites further suggests that this relationship was largely explained by an increase in synchronization of dendritic activity during spindles. Interestingly, this effect was specific to dendrites as L2/3 and L5 cell bodies did not show such correlation.

Our results support the current hypothesis of a direct link between spindles and dendritic activity regulation and further reveal an important, yet unexplored, functional coupling between spindle and beta oscillations (15-30Hz). Further (and ongoing) experiments probing the influences of experience on this relationship will reveal important information on the physiology of spindles and their role in learning and memory.

References:
1. Contreras, D., Destexhe, A. & Steriade, M. Intracellular and computational characterization of the intracortical inhibitory control of synchronized thalamic inputs in vivo. J. Neurophysiol. 78, 335-350 (1997). 2. Sejnowski, T. J. & Destexhe, A. Why do we sleep? Brain Res. 886, 208-223 (2000).

Contact email address: j.seibt@surrey.ac.uk

Poster number: P-W114
Theme: Learning & memory

Reconsolidation of Episodic Memory Processing

Authors: Kai Rong Tay, Jonathan Lee, Maria Wimber - *Psychology University of Birmingham*

Memory reactivation can lead to two phenomena: memory updating / reconsolidation with possibility of having inaccurate memories and memory strengthening. In Study 1, we attempted to replicate previous findings of episodic-like memory reconsolidation that re-exposure to the initial learning context is sufficient to induce reconsolidation. In a visual list-learning paradigm, participants learned 2 lists in different ways on 2 days. The experimental group learned both lists in the same room and with the same experimenter. The control group learned the two lists in different rooms with different experimenters. At test, participants were returned to the original context and recalled images from the 1st day of learning. ANOVA unexpectedly showed no difference in intrusions of Day 2 items into Day 1 recall between Experimental and Control groups, thereby failing to replicate published findings. While the Control Group had poorer recall of Day 1 items compared to a no interference control, performance in the Experimental Group was preserved. This may reflect an effect of training context re-exposure to strengthen the memory and mitigate against the deleterious impact of interfering material. In Study 2, we tested directly the capacity of memory reactivation to facilitate memory strengthening. Participants learned visual object-scene paired associated and two days later were subjected to a retrieval test and/or further learning in the same room and with the same experimenter. When subsequently tested on the paired associate recall, participants that received retrieval followed by relearning, relearning followed by retrieval, or two relearning episodes all had greatly improved performance. Groups that received one or two retrieval episodes performed as poorly as a control group, with all three groups showing evidence of memory decay. Finally, participants that received a single relearning episode performed at an intermediate level, with mild improvement. The common effects of retrieval-relearning, relearning-retrieval and relearning-relearning to strengthen episodic memory may reflect different underlying processes, one or more of which might be related to memory reconsolidation.

Contact email address: kxt491@student.bham.ac.uk

Poster number: P-W115
Theme: Learning & memory

Engagement of mGlu5 receptors facilitates electrically but not optically induced NMDA receptor-dependent hippocampal LTD by recruiting more GluN2B

Authors: Kenneth J. O'Riordan, Neng-Wei Hu, Michael J. Rowan - *Department of Pharmacology & Therapeutics Trinity College Dublin*

Synaptic long-term depression (LTD) is believed to underlie critical mnemonic processes in the adult hippocampus. Considerable controversy exists over the roles of the metabotropic and ionotropic actions of glutamate in the induction of synaptic LTD by electrical low frequency stimulation (LFS), based largely on studies in hippocampal slices from very young animals. Here we examined the requirement for metabotropic (mGlu) and NMDA glutamate receptors in LTD induction by either electrical or optical LFS. Approximately 2-4months after transfection with AAV5-CaMKIIa-hChR2(H134R)-EYFP in the dorsal hippocampus, electrically or optically evoked synaptic transmission at CA3-to-CA1 synapses was recorded under urethane anaesthesia. Application of either electrical or optical 900 pulse 1Hz LFS, with the intensity increased to 95% maximum amplitude, induced robust and stable electrical (eLTD) and optical (oLTD) LTD, respectively. We found that: (i) On their own neither the competitive NMDAR antagonist CPP, nor the

selective mGlu5R antagonist MTEP administrated via systemic injection had an effect on eLTD. However, the systemic co-administration of CPP and MTEP blocked eLTD. (ii) Consistent with the CPP results, whereas the negative allosteric modulator of GluN2B, Ro 25-6981, alone failed to significantly alter LTD the same dose of Ro 25-6981 given together with MTEP, greatly attenuated eLTD. (iii) Administration of relatively high doses of NMDAR antagonists D-AP5 and Ro 25-6981 locally near the hippocampus, via the i.c.v. route, the magnitude of eLTD was greatly attenuated. (iv) Standard doses of NMDAR antagonists CPP, D-AP5 and Ro 25-6981 that failed to prevent eLTD, strongly attenuated oLTD. (v) In the animals pretreated with the mGlu5R positive allosteric modulator VU 0360172, a peri-threshold electrical 300 pulse 1Hz LFS facilitated robust eLTD but a peri-threshold optical 300 pulse 1Hz LFS only induced a transient depression of synaptic transmission. The present data provide strong evidence in the living animal that the engagement of mGlu5 receptors during electrical, but not optical, low frequency conditioning stimulation increases ion flux via the recruitment of more GluN2B-containing NMDA receptors, thereby boosting LTD induction.

Contact email address: keoriord@tcd.ie

Poster number: P-W116
Theme: Learning & memory

Phenotypic differences in performance of a three choice serial reaction time task (3-CSRTT) in a non-rodent species

Authors: Kirsty Roberts, Andrew Hemmings - *CEMS Royal Agricultural University*, Sebastian McBride - *IBERS Aberystwyth Unversity*, Matthew Parker - *School of Health Sciences and Social Work University of Portsmouth*

Rationale: Large animal models of neurocognitive dysfunction hold unique advantages over rodent models, e.g. functional heterogeneity of brain structures and species longevity. Recently, the use of the horse as a complementary animal model has been considered, with animals successfully achieving learning criterion of an adapted 3-choice serial reaction time task (3-CSRTT). To examine the usefulness of an equine model further, a cohort of high, medium and low dopamine horses not yet exhibiting symptoms of spontaneous neural dysfunction (e.g. hyperdopaminergic stereotypy or hypodopaminergic pituitary pars intermedia dysfunction) were studied to determine if phenotypic differences, if apparent, could be detected by our adapted 3-CSRTT.

Methods: High (n=10), medium (n=10), and low (n=10) dopamine horses were recruited utilising spontaneous blink rate (SBR; Low<440; Medium 440-622; High >622 blinks/30min). All horses were trained on the 3-CSRTT with a pre-established training regimen. Following learning criterion attainment, six test sessions were utilised to obtain data regarding omission and commission errors, as well as impulsive and compulsive responding.

Results: One high and two low animals did not reach learning criterion and were removed from subsequent analysis. Repeated measures ANOVA indicated performance parameters (accuracy, impulsive responding, compulsive responding, commission errors, omission errors) between the six test sessions were not significantly different for any group ($p>0.05$). However, one-way ANOVAs highlighted significant differences between the cohorts over the six test sessions (Table 1). No significant differences were apparent between cohorts for omission and commission errors.

Conclusions: The adapted 3-CSRTT for equine use is sensitive to differences in responding between dopamine phenotypes. Furthermore, the significant increase in compulsive and impulsive responding in the non-symptomatic high dopamine animals could indicate that such behaviour patterns may arise prior to the development of the hyperdopaminergic condition stereotypy. Subject to further investigation, the utilisation of impulsive and compulsive responding may prove fruitful in screening methods to identify those at risk of developing stereotypic behaviours.

Table 1. Statistically significant 3-C SRTT parameters over the six test sessions ($p<0.05$). NB (-) indicates non-significance; data sharing the same superscript for a parameter within sessions are not statistically significant.

Session	Group	Duration±SD (s)	Accuracy±SD (%)	Impulsive Responses±SD (%)	Compulsive Responses±SD
1	Low	-	80.00±7.97^{a}	7.50±5.56^{a}	-
	Medium	-	80.00±15.07^{a}	8.00±7.57^{a}	-
	High	-	66.67±7.45^{b}	17.73±10.50^{b}	-
2	Low	-	-	-	5.13±2.90^{a,b}
	Medium	-	-	-	3.10±2.60^{b}
	High	-	-	-	9.44±6.62^{a}
3	Low	412.46±25.16^{a}	77.50±16.31^{a}	11.67±67±14.58^{a}	-
	Medium	415.14±21.12^{a}	82.67±13.41^{a}	3.34±3.52^{a}	-
	High	380.40±37.35^{b}	59.26±18.09^{b}	28.15±22.30^{b}	-
4	Low	412.60±23.33^{a}	76.67±17.09^{a}	5.83±7.51^{a}	4.50±2.62^{a}
	Medium	410.44±24.26^{a}	80.67±11.09^{a}	3.34±3.52^{a}	4.40±3.50^{a}
	High	379.51±28.33^{b}	59.26±17.46^{b}	25.18±16.92^{b}	11.11±5.42^{b}
5	Low	-	-	11.67±8.54^{a,b}	3.75±2.96^{a}
	Medium	-	-	4.00±4.66^{a}	2.90±2.69^{a}
	High	-	-	20.00±11.55^{b}	9.67±6.00^{b}
6	Low	-	-	7.50±9.72^{a,b}	6.00±4.00^{a,b}
	Medium	-	-	2.00±3.22^{a}	2.30±2.50^{a}
	High	-	-	17.78±20.27^{b}	12.00±11.36^{b}

Contact email address: kirsty.roberts@student.rau.ac.uk

Poster number: P-W117
Theme: Learning & memory

The Cerebellar Basis of Instrumental Learning in the Human Brain: Ultra-High Field (7T) Event-Related Functional MRI

Authors: Mark Mikkelsen - *Psychology Royal Holloway, University of London*, Samuel A. Hurley - *University of Wisconsin Department of Neuroscience,* Stuart Clare - *Oxford Centre for Functional MRI of the Brain (FMRIB), Nuffield Department of Clinical Neurosciences University of Oxford*, Narender Ramnani - *Department of Psychology Royal Holloway, University of London*

The cerebellum and cortical motor areas are interconnected in a closed anatomical loop that contributes to the acquisition of motor skills. Other parts of the cerebellum, in lobule HVIIA, are connected with the prefrontal cortex and could sustain more complex forms of learning. During instrumental rule learning, conditioned stimuli (CS) can be paired arbitrarily with actions. Using 3T fMRI, we have previously shown that such CS evoke activity in lobule HVIIA, but limited signal-to-noise makes it difficult to understand the anatomical detail in single subjects. Here, we used 7T event-related fMRI to achieve greater sensitivity and anatomical detail than previously has been possible.

Fifteen adults (21–39 y; 6 F) underwent 18.5 min of 7T fMRI scanning (1.5-mm isotropic voxel). A high-resolution structural image was also acquired (0.7mm isotropic voxel). Subjects were required to form associations between a set of arbitrary visual CS and one of four finger movements using trial-and-error learning. CS were followed by a variable delay (0.12–3.85s), a Go! signal and visual feedback (correct/incorrect). In control trials, the visual cue directly specified the movement and so no arbitrary rules were learned.

The frequency of correct responses increased during learning. Activity time-locked to the onset of symbolic instruction cues was compared with that of control cues. Activations were present bilaterally in three main locations (Fig. 1) that included mostly lobule HVIIA. First, in an area that extended across the superior posterior fissure across lobules HVI and HVIIA, second, in the vermal parts

of lobule HVII, and finally in lobule HVIIA at the border with lobule HVIIB. The anatomical consistency of these effects is visible in three cases presented in Fig. 1a.

Our results provide further support that areas of the cerebellum connected with the prefrontal cortex are sensitive to instruction cues that acquire associative properties during instrumental learning. This study is the first to use 7T event-related fMRI to understand cerebellar excitability changes related to instrumental learning. The findings verify previous experiments but go further by providing anatomical detail at high resolution in single subjects.

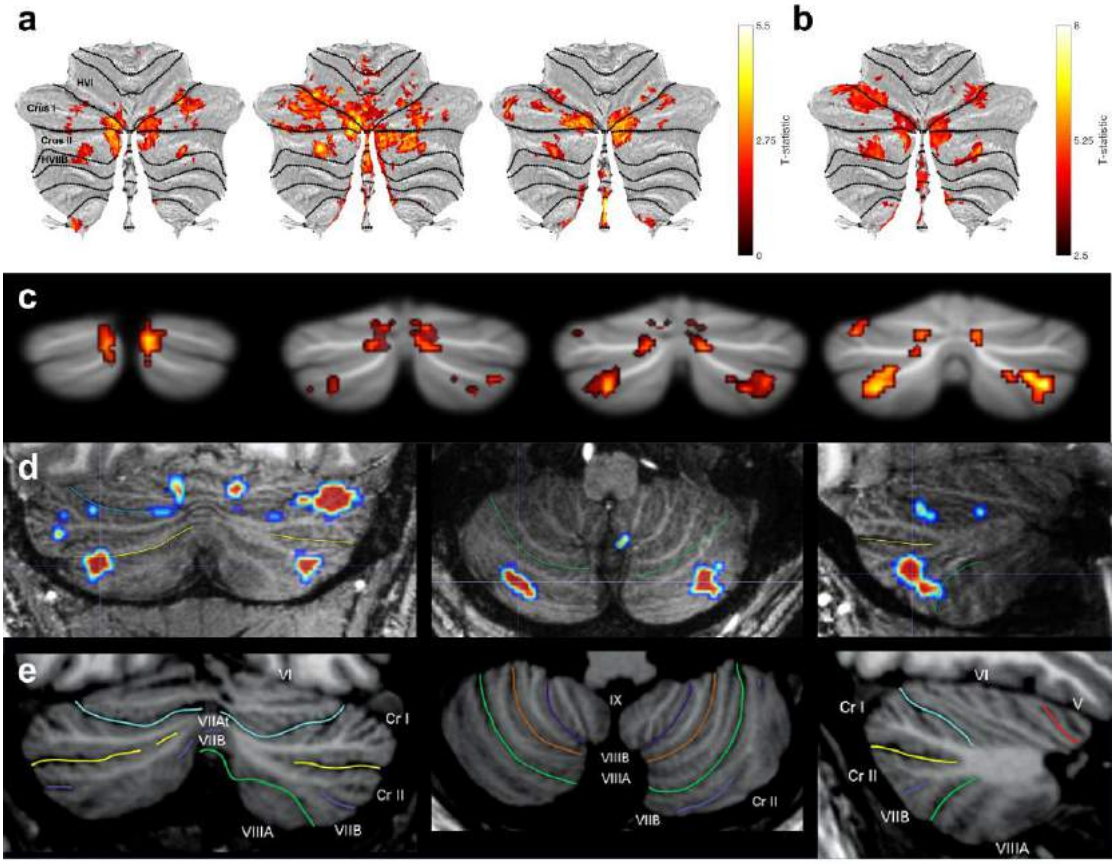


Fig. 1. (**a**) Thresholded activations, largely in lobule HVIIA (Crus I/II), in three individual subjects superimposed onto a cerebellar flatmap. Group activation map superimposed onto a cerebellar flatmap (**b**) and onto serial coronal sections of a template brain (**c**). (**d**) Individual activation map of one subject superimposed onto the structural image of that individual (coronal, axial and sagittal sections through activation in lobule HVIIA (Crus II) indicated by crosshairs). (**e**) Corresponding sections through cerebellar atlas of Schmahmann et al. (2000), *MRI Atlas of the Human Cerebellum*, Academic Press. Yellow line, horizontal fissure; green line, prepyramidal fissure. For all activated voxels, $p < 0.001$, uncorrected.

Contact email address: n.ramnani@rhul.ac.uk

Poster number: P-W118
Theme: Learning & memory

Proactive Control and Episodic Retrieval Orientation

Authors: Michael Siena - *Psychology The University of Edinburgh*, Petar Raykov - *School of Psychology University of Sussex,* Alexa Morcom - *Psychology The University of Edinburgh*

The recovery of information from episodic memory can be influenced by goal-directed control applied prior to the point of retrieval. In two event-related potential (ERP) studies we investigated the links between this preretrieval control and proactive control abilities assumed to operate across multiple cognitive domains. We assessed the relation between retrieval orientation – the degree to which retrieval cue processing varies according to retrieval goals – and established measures of proactive attentional control (the AX-Continuous Performance Task; AX-CPT). In Experiment 1, participants made either an Artist, a Function or a Pleasantness judgement on words at study, then at test had to accept items studied in just one of these tasks as “targets” (other studied items and new items were “non-targets”). In Experiment 2, they made either living/non-living or indoor/outdoor judgments at study for words presented to the left or right of the screen. At test, they had to accept items as targets either according to screen location or the judgement performed at study. To measure retrieval orientation, ERPs to correctly rejected new items were contrasted according to the type of information targeted at retrieval, in a priori time windows based on previous studies using these

tasks. In Experiment 1, both proactive control measures from the AX-CPT and the magnitude of ERP retrieval orientation effects from 500-700 ms predicted ability to discriminate targets from non-targets in the exclusion task. Individuals with better target performance on the AX-CPT also showed larger ERP retrieval orientation effects. In Experiment 2, individual differences in the magnitude of ERP retrieval orientation effects from 400-800 ms were again associated with the engagement of proactive control on the AX-CPT. In both studies, ERP retrieval orientation effects were more pronounced in individuals who engaged proactive control to a greater degree, although there were differences between experiments in the AX-CPT measures showing these associations. The results of both experiments suggest a relationship between episodic memory control via retrieval orientation and more general proactive cognitive control processes.

Contact email address: michaelsiena@hotmail.co.uk

Poster number: P-W119
Theme: Learning & memory

Methylphenidate modulates experience-based, but not vicarious, learning

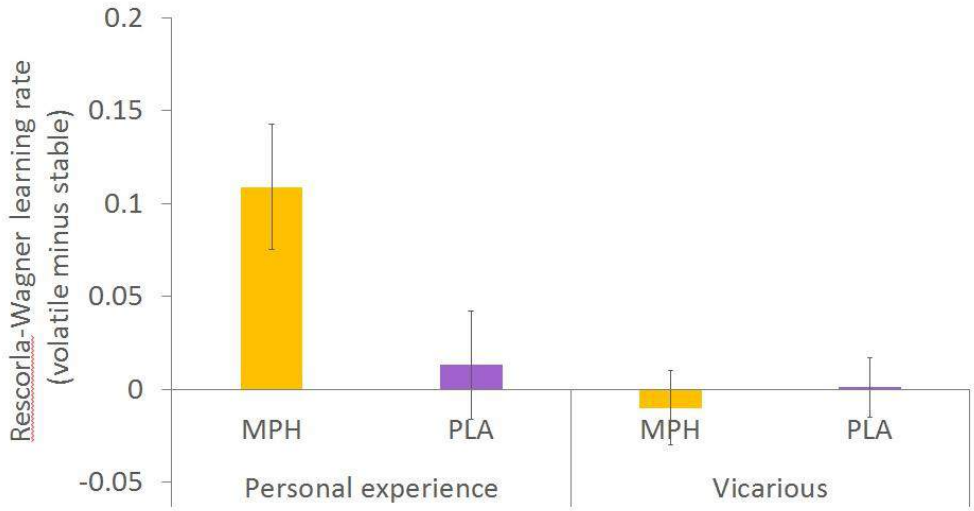
Authors: Jennifer Cook - *Psychology University of Birmingham*, Hanneke den Ouden, Monja Froböse, Jennifer Swart, Dirk Geurts - *Donders Centre for Cognitive Neuroimaging Radboud University*, Sean James Fallon - *Department of Experimental Psychology University of Oxford*, Roshan Cools - *Donders Centre for Cognitive Neuroimaging Radboud University*

Previous work [1] has implicated a network of brain regions that is highly innervated by the catecholamine system in experience-based, but not vicarious, learning (learning from an indirect source of information such as advice from a colleague). Such results raise the possibility that these two types of learning are underpinned by dissociable neurochemical mechanisms – a controversial suggestion consistent with the hypothesis that humans have evolved 'special' mechanisms for social learning. Here we investigate whether:
1) catecholamine system modulation has dissociable effects on experience-based and vicarious learning
2) dissociable effects seen in (1) are due to the social nature of vicarious learning

Experiment 1: Participants took methylphenidate (MPH) - which increases dopamine and noradrenaline in prefrontal and striatal [3] areas - and placebo (PLA) according to a cross-over, double-blind, within subject design. All participants completed a learning task in which they learned outcome probabilities in stable and volatile environments. Outcome probabilities could be learned via one's own personal experience of reward outcomes, via vicarious learning from a social source, and/or by combining both personal experience and social information. Learning rates for personal-experience based and vicarious learning in volatile and stable environments were estimated. Relative to PLA, MPH improved experience-based learning, but not vicarious learning. More specifically, under MPH participants were better able to adjust to the environment, learning fast when the environment was fast-changing (volatile) and slow when the environment was stable.

Experiment 2: The procedure was identical to Experiment 1 except the source of vicarious learning was non-social in nature (i.e. advice originated from a system of rigged roulette wheels). As in Experiment 1, MPH improved experience-based, but not vicarious, learning. Thus, MPH has dissociable effects on experience-based and vicarious learning that can be observed irrespective of whether the source of vicarious learning is social in nature.

[1] Behrens ea. (2008) Nature,456,245–249.
[2] Volkow ea. (2001) J Neurosci,21,RC121



Contact email address: j.l.cook@bham.ac.uk

Poster number: P-W120
Theme: Genetics & epigenetics

Non-monotonic phenotypes and gene expression changes in an allelic series of Chd8-deficient mice

Authors: Albert Basson - *Craniofacial Development and MRC Centre for Neurodevelopmental Disorders King's College London*, Philipp Suetterlin, Kimberley Riegman, Shaun Hurley, Conor Mohan - *Craniofacial Development King's College London*, Angela Caruso - *Cell Biology and Neuroscience Istituto Superiore di Sanità*, Jacob Ellegood - *Medical Biophysics Sickkids*, Ivan Crespo-Enriquez - *Craniofacial Development King's College London*, Caterina Michetti - *Istituto Superiore di Sanità Istituto Superiore di Sanità*, Robert.ellingford - *Craniofacial Development King's College London*, Olivier Brock, Alessio Delogu - *Basic and Clinical Neuroscience King's College London,* Philippa Francis-West - *Craniofacial Development King's College Londo*n, Jason Lerch - *Medical Biophysics Sickkids*, Maria Luisa Scattoni - *Cell Biology and Neuroscience Istituto Superiore di Sanità*, Cathy Fernandes - *MRC Social, Genetic & Developmental Psychiatry Centre King's College London*

Truncating CHD8 mutations are amongst the highest confidence autism risk factors identified to date. To investigate how reduced Chd8 gene dosage may predispose to autism, we constructed a mouse Chd8 allelic series. Whereas the pan-neuronal, homozygous deletion of Chd8 results in brain hypoplasia, we find that Chd8 heterozygous mice display subtle brain hyperplasia and only minor gene expression changes. A small additional decrease of Chd8 expression in Chd8 hypomorphs causes robust changes in the expression of 168 autism-associated genes and hyperplasia of several autism-associated brain areas. Unexpectedly, neither Chd8 heterozygous nor hypomorphic mice display autism-like behaviours. Together, these data show that gene expression and brain growth respond in a non-monotonic fashion to changes in Chd8 expression. We propose that CHD8 haploinsufficiency represents a sensitised genetic background that is not necessarily sufficient to cause autism, but may strongly predispose to autism by reducing the threshold for additional autism risk factors.

Contact email address: albert.basson@kcl.ac.uk

Poster number: P-W121
Theme: Genetics & epigenetics

Brain-derived Neurotrophic Factor (BDNF) and Epigenetics in Skeletal Muscle after Chronic Stroke: Effects of Exercise Training

Authors: Alice S. Ryan, Huichun Xu, Frederick M. Ivey, Richard F. Macko, Charlene E. Hafer-Macko - *University of Maryland School of Medicine, Division of Gerontology*

Background: Stroke leads to long-term disability and cognitive dysfunction. Improved neurotrophic factor signaling is one hypothesis for the positive effects of physical activity on cognition. It is unknown if BDNF changes with exercise in stroke. We hypothesize that BDNF is involved in the skeletal muscle changes post-stroke and exercise exerts beneficial effects through epigenetic regulation of BDNF expression.

Purpose: 1) To compare paretic (P) vs. non-paretic (NP) skeletal muscle BDNF and the effects of resistive training (RT) on systemic and skeletal muscle BDNF mRNA expression in stroke; 2) To compare the DNA methylation profile for BDNF and BDNFAS (BDNF Antisense RNA) between P and NP muscle and the effects of aerobic training (AEX) on DNA methylation in stroke.

Methods: Chronic stroke survivors (50-76 years) had a fasting blood draw and 12-week (3x/week) RT (n=16). Bilateral vastus lateralis muscle tissue biopsies (n=10) were conducted and BDNF expression determined by RT-PCR. A separate group of five male older chronic stroke survivors completed 6-months of AEX (3x/week) and had bilateral muscle biopsies. DNA methylation status in gene BDNF and BDNFAS was assessed by Illumina 450k Methylation array.

Results: Paretic muscle had ~45% lower BDNF expression than NP muscle (6.79±1.30 vs. 10.52±2.06 AU, $P<0.05$) and exhibited differential methylation status in the DNA sequences of BDNF (3 CpG sites, $P=0.016$ to 0.044) and BDNFAS (1 CpG site, $P=0.016$) compared to NP. Bilateral leg strength and muscle area increased with RT ($P<0.05$). Plasma BDNF increased 25% with RT. Muscle BDNF mRNA expression did not significantly change after RT (P: 7.21±1.38 vs. 7.06±1.85 AU and NP:11.39±2.12 vs. 7.84±1.32 AU). DNA methylation in BDNFAS in P muscles relative to NP increased after AEX in P ($P=0.017$).

Conclusions: This is the first evidence that BDNF skeletal muscle expression is reduced by hemiparesis, which may be caused by methylation alterations on the DNA sequence of BDNF and BDNFAS gene. Preliminary findings indicate that AEX increases methylation in BDNFAS gene, which presumably could regulate the expression of BDNF. Future research could examine if changes in epigenetics with exercise training are associated with improved cognitive ability in stroke survivors.

Contact email address: aryan@som.umaryland.edu

Poster number: P-W122
Theme: Genetics & epigenetics

A knock-out mouse model for the microcephaly-associated Trappc9 gene and its epigenetic regulation by genomic imprinting.

Authors: Antonius Plagge, Michela Pulix - *Cellular and Molecular Physiology University of Liverpool*, Thomas Leather - *Centre for Preclinical Imaging University of Liverpool*, Kirsty Ingram - *Cellular and Molecular Physiology University of Liverpool*, Philippe Arnaud - *Gred CNRS Université Clermont Auvergne*, Harish Poptani - *Centre for Preclinical Imaging University of Liverpool*

Homozygous mutations of TRAPPC9 in humans cause a neurodevelopmental disorder characterised by microcephaly, intellectual disability, white matter hypoplasia, speech impairments and developmental delays. These symptoms are consistent with Trappc9 expression in neurons, although it is also found in several peripheral tissues. Trappc9 forms part of the trafficking protein particle II complex. It is implicated in vesicle transport at the ER / Golgi and also interacts with the dynactin/dynein motor complex that mediates retrograde transport and signalling along microtubuli.

The Trappc9 gene is part of a cluster of imprinted genes on mouse chromosome 15 and human chromosome 8. Imprinted genes are regulated by epigenetic marks, which are established differentially in male and female germ cells and maintained in the developing embryo and adult tissues. Differential DNA methylation on one of the parental alleles results in parent-of-origin dependent, monoallelic gene expression.

Here, we describe knock-out (KO) mice for Trappc9, which we found to be viable without major embryonic or postnatal deficiencies. However, 3-months old female KOs show a significant 20% increase in body weight. Brain weights in male and female KOs are significantly reduced by 10%. This was confirmed in measurements of total brain volume by high-resolution µMRI using a 9.4T magnet. Initial data indicate a 15% reduction in Sox2-positive neural progenitor cells in the hippocampal dentate gyrus.

To analyse imprinted, allele-specific expression of Trappc9 we quantified exonic SNPs in brain and kidney cDNA from C57BL/6J x JF1 strain intercrosses by pyrosequencing. 70% of Trappc9 RNA in brain was found to be derived from the maternal allele, confirming genomic imprinting of the gene. In kidney, equal biallelic expression was detected. Analysis of DNA methylation at CpG-islands at the 5'-end of Trappc9 by pyrosequencing of bisulphite-treated brain DNA showed very low levels (10%) of CpG methylation.

In conclusion, Trappc9 KO mice reproduce a microcephaly phenotype, similar to human patients. Trappc9 is imprinted in the mouse brain with preferential (70%) expression from the maternal allele. Its epigenetic regulation is mediated by other mechanisms than promoter CpG-island methylation.

Contact email address: a.plagge@liverpool.ac.uk

Poster number: P-W123
Theme: Genetics & epigenetics

Single nucleotide polymorphisms of GRIN2B are associated with major depressive disorder – a preliminary study in a Thai sample

Authors: Benjamard Thaweethee - *Department of Anatomy and Centre of Excellence in Medical Biotechnology, Faculty of Medical Science, and Biomolecular Sciences Research Centre Naresuan University and Sheffield Hallam University*, Sirijit Suttajit - *Department of Psychiatry Faculty of Medicine, Chiang Mai University*, Samur Thanoi - *Department of Anatomy and Centre of Excellence in Medical Biotechnology, Faculty of Medical Science Naresuan University*, Caroline F. Dalton - *Biomolecular Sciences Research Centre Sheffield Hallam University*, Gavin P. Reynolds - *Department of Anatomy and Centre of Excellence in Medical Biotechnology, Faculty of Medical Science , and Biomolecular Sciences Research Centre Naresuan University and Sheffield Hallam University*, Sutisa Nudmamud-Thanoi - *Department of Anatomy and Centre of Excellence in Medical Biotechnology, Faculty of Medical Science Naresuan University*

Background: Major depressive disorder (MDD) affects around 15% of people worldwide, and MDD patients have a high risk of suicide. Genetic studies in twins indicate that genetic factors may be important in MDD and suicidal behaviour. Genetic variation in genes coding for subunits of the glutamate NMDA receptor (GRIN) has been associated with other psychiatric disorders such as schizophrenia and bipolar disorder, but have been little studied in MDD, despite increasing evidence for glutamatergic dysfunction in the disease. Therefore, this study aimed to evaluate the association of single nucleotide polymorphisms (SNPs) in GRIN1 and GRIN2B with MDD in a Thai sample.

Methods: Subjects included patients with MDD (n=100) (including non-suicide MDD (n=50) and suicide MDD (n=50)) and controls with no history of psychiatric disorder (n=100). DNA was extracted from FTA dried blood spots and genotyped with TaqMan™ SNP Genotyping Assays. Five SNPs were selected to study: rs4880213 in GRIN1 and rs1805502, rs890, rs3764030 and rs1019385 in GRIN2B, all of which have been reported in association with psychiatric disorders and/or are potentially functional.

Results: We found significant differences in allele and genotype frequencies of rs890 between the MDD and control groups (P=0.009 and P=0.022, respectively). Furthermore, the genotype frequency of rs3764030 was significantly associated with MDD (P=0.013). In addition, strong linkage disequilibrium (LD) was observed between rs1805502 and rs890 (D'=0.82), and rs3764030 and rs1019385 (D'=0.97). We found that the AA haplotype of rs1805502 and rs890 in the MDD group was significantly higher (P=0.005), while the frequency of AC haplotype was significantly lower than the control group (P=0.014). Interestingly, the genotype frequency of rs3764030 was also significantly associated with suicide attempt in MDD (P=0.043).

Conclusions: This preliminary study is limited by the relatively small sample size and needs replication in a substantially larger sample. Further studies will address this and explore the relationship of the genetic association with treatment response. However, these findings do provide initial evidence for variation in the gene for the NMDA receptor 2B subunit in risk for MDD.

Contact email address: benjamard.thaweethee@gmail.com

Poster number: P-W124
Theme: Genetics & epigenetics

Can Mammalian-wide Interspersed Repeats (MIRs) impact upon epilepsy? (bioinformatics based approach)

Authors: Gill Spoor

Mammalian-wide interspersed repeats (MIRs) integrated into the mammalian genome during the Mesozoic period; their continued recognisability, in spite of the passage of time, suggests they may now contribute to their host's genome. As a transposable element (TE), MIRs historically duplicated and were dispersed throughout the host's genome, a feature that potentially ratifies and impacts upon internetwork regulation. Despite this, their potential impact with respect to epilepsy, a prevalent condition associated with neuronal dysregulation, has not been fully considered.

To further current knowledge, this study drew upon databases and repeat masking tools in order to identify epilepsy associated genes that contain MIRs. Given the ultimate aim was to identify the role of MIRs, attention was then afforded to those occupying coding regions. In the cohort examined, MIRs were found exclusively within the 3' UTRs of qualifying genes.

The second element, as mentioned, sought to identify the impact MIRs may have, to this end several lines of inquiry were enacted upon.

• Firstly, co-occurrences between MIRs and mutated regions were sought, however none were found.
• The original MIRs were then compared to the MIRs identified in the human gene, these comparisons showed degradation typically beyond 50%, suggesting the original roles fulfilled by the MIR have likely been compromised.
• Using the bioinformatics tool ClustalW, MIRs were sought across divergent mammalian species, where found, the then aligned sequences were scanned for motifs, revealing several capable of impacting upon gene regulation.

The culmination of results suggests that some epilepsy associated genes have exapted MIRs into positions of regulatory influence. However, further research is recommended to discern the full extent of their impact upon their host genes and indeed upon the condition

Contact email address: gillspoor@hotmail.co.uk

Poster number: P-W125
Theme: Genetics & epigenetics

The epigenetic regulation of cerebellar development

Authors: Kimberley Riegman - *Craniofacial Development and Stem Cell Biology King's College London*, Danielle. E. Whittaker - *Clinical services Royal Veterinary College*, Conor Mohan - *Craniofacial Development and Stem Cell biology King's College London,* Charlotte George - *CGAT University of Oxford*, Cameron Osborne - *Department of genetics and molecular medicine King's College London*, Albert Basson - *Craniofacial Development and Stem Cell Biology King's College London*

Development of the cerebellum is under tight temporal control and perturbances at different developmental stages lead to discernible cerebellar phenotypes. Previous work in our group has demonstrated a key role for the ATP-dependent chromatin remodeller CHD7 (chromodomain-helicase-DNA-binding protein 7) in mouse cerebellar development. Deletion of Chd7 from mouse cerebellar granule cell precursors (GCps) results in cerebellar hypoplasia, developmental delay, motor deficits and down-regulation of Reln, a gene essential for cerebellar development. In this project we sought to establish the underlying cause of the cerebellar hypoplasia in these mice and the mechanisms by which CHD7 regulates gene expression in GCps and in particular Reln. We demonstrated that Chd7 deficiency in these cells results in reduced proliferation and increased apoptosis of GCps during early postnatal development. Through ATACseq analyses we found that CHD7 functions primarily to maintain an open “accessible” chromatin state at the Reln locus and at many other loci in GCps. Finally, we used promoter capture Hi-C in primary GCps to identify putative long-range regulatory elements. Preliminary findings on regulatory interactions of Reln and other genes involved in cerebellar development will be discussed.

Contact email address: kimberley.riegman@kcl.ac.uk

Poster number: P-W126
Theme: Genetics & epigenetics

Polygenic Risk Score for Schizophrenia as a Predictor of Symptoms and Treatment Response in Major Depressive Disorder

Authors: Nadya Rebar - *School of Biological and Chemical Sciences Queen Mary, University of London*

Shared genetic factors between Schizophrenia and Major Depressive Disorder (MDD) have been documented through multiple studies, enabled by the increased use of genome-wide association studies (GWAS). Such studies are limited in their view of psychiatric disorders as sums of their total parts; focusing on categorical symptoms within these disorders can provide a more precise understanding of comorbidity and the influence of genetic abnormalities on mental health. This study aims to explore the polygenic risk score for Schizophrenia (PGRS-Sz) as a predictor of symptoms and treatment response in patients with MDD. Data from the Psychiatric Genomics Consortium’s GWAS on Schizophrenia was used to calculate PGRS-Sz as the base phenotype for analysis on data collected by the genome-based therapeutic drugs for depression (GENDEP) study (http://gendep.iop.kcl.ac.uk), which provided the following target phenotype data: depression scores on the Montgomery-Asberg Depression Rating Scale, the Hamilton Depression Rating Scale, and the Beck Depression Inventory, and cognitive, neurovegetative, core mood, observed mood, pessimism, anxiety, anhedonia, sleep, and appetite symptom scores. A series of multiple linear regressions was calculated to predict

each target phenotype based on PGRS-Sz. No significant regressions were found. Next, a series of mixed effects logistic regression models was estimated to explore PGRS-Sz as a predictor of treatment response in patients treated with an SSRI, a tricyclic, and both, using each target phenotype in turn as a fixed effect. No significant model was found for patients treated with the SSRI, but significant models were found at various thresholds for core mood, anxiety, and appetite in patients treated with the tricyclic and both drugs, and observed mood and pessimism in patients treated with the tricyclic ($p<0.05$). The results suggest that PGRS-Sz may not be a reliable predictor of severity of MDD and its symptoms, nor for treatment response to SSRIs. However, PGRS-Sz may be a predictor of change in core mood, observed mood, pessimism, anxiety, and appetite in response to tricyclic treatment, and of change in core mood, anxiety, and appetite in response to a combination of both treatments within a short period of time.

Contact email address: n.rebar@se14.qmul.ac.uk

Poster number: P-W127
Theme: Genetics & epigenetics

DNA Base Modifications in Brain Health and Disease

Authors: Poppy Winlow - *School of Biosciences University of Nottingham*

For most of molecular biology's era methylation of cytosine (5-methyldeoxycytidine/ 5mdC) was thought to be the only base modification in mammalian DNA formed by enzymatic reactions. The catalogue of known epigenetic DNA modifications has expanded and includes three cytosine methylation-derivatives (5hmdC, 5fdC, and 5cadC), as well as methylation of adenosines (6mdA). We are currently measuring and mapping 5hmdC as well as 6mdA in DNA isolated from the central nervous system. We find that nuclear DNA of the cerebellum from individuals with Parkinson's Disease has significantly higher levels of 5hmdC when compared to age-matched DNA samples isolated from individuals who were not affected by this progressive neurological condition. We are in the process of exploring how different enzymes, cellular conditions and environmental stressors may influence the epigenome and thereby be associated, or even cause, neurological disorders.

Contact email address: poppy.winlow@nottingham.ac.uk

Poster number: P-W128
Theme: Genetics & epigenetics

Inhibiting DNA methylation elicits divergent behavioral outcomes in females exposed to different maternal caregiving environments

Authors: Samantha Keller, Tiffany Doherty, Tania Roth - *Psychological and Brain Sciences University of Delawar*

The maternal caregiving environment has critical implications for development of the brain and behavioral trajectories in both humans and rodents. For example, exposure to maltreatment by the caregiver is associated with a variety of negative outcomes in adulthood, including deficits in cognitive function and increased prevalence rates of certain psychiatric illnesses. Epigenetic mechanisms, which involve changes in genetic expression without alterations to the underlying genomic sequence, are dynamic throughout the lifespan and offer one potential mechanism via which it is possible for these early life experiences to alter adult phenotype. DNA methylation is one type of epigenetic modification involving the addition of methyl groups to cytosines on DNA that is typically linked with gene repression. Using a rodent model of caregiver maltreatment, our lab has detected alterations in DNA methylation throughout the brain of maltreated animals. These epigenetic alterations coincide with behavioral changes in these maltreated animals, including deficits in novel object recognition memory and maternal behavior. However, the role of epigenetic alterations resulting from maltreatment exposure in mediating these aberrant behavioral outcomes is unknown. In the current study, we administered Zebularine, a drug that has been shown to rescue maltreatment-induced DNA methylation, to adult female animals. Preliminary data suggests that administration of Zebularine rescues deficits in both maternal behavior and novel object recognition in females with a history of maltreatment. Interestingly, drug treatment disrupts maternal behavior and novel object recognition in females with a history of normal maternal care during infancy. We likewise found differences in levels of DNA methylation throughout the brain in brain regions relevant for maternal behavior, including the medial preoptic area, in dams that had been maltreated by their caregiver in infancy that were normalized by Zebularine treatment. Data suggest that altering DNA methylation in adulthood is capable of rescuing brain and behavioral outcomes of experiencing caregiver maltreatment. Additionally, this drug has divergent effects in animals dependent upon infant caregiver experience.

Contact email address: skeller@psych.udel.edu

Poster number: P-W129
Theme: Genetics & epigenetics

Investigating the relationship between GABAB receptor 1 genotype and gene expression in temporal lobe epilepsy.

Authors: Sarah Rennicks - *Biomedical Sciences Research Centre Sheffield Hallam University*

Temporal lobe epilepsy (TLE) is a neurodegenerative disease characterised by recurrent, unprovoked focal seizures that originates in the temporal lobes. In recent years, gamma-aminobutyric acid receptor 1 (*GABBR1*) has been implicated as a novel target in the pathogenesis of TLE. Pharmacogenomics has revolutionised the approach to medicine, allowing single nucleotide polymorphisms (SNPs) to inform response to therapy, much needed for this drug resistant neurodegenerative disease. To assess the contribution of *GABBR1* in TLE pathogenesis two SNPs (rs29218, rs29220) were selected and genomic DNA was extracted using Qiagen QIAmp Mini Kit (250) from samples from 15 patients whom had been diagnosed with TLE. Genomic DNA was genotyped and analysed using StepOnePlus RT-PCR. rs29218 is a single base change A7265G within the promoter region of *GABBR1*, with the G allele present in 27% of the TLE patients. Sequence analysis of the promoter region around rs29218 indicate that this SNP alters the binding of the transcription factor USF-1, previous data has shown that USF-1 deficient mice present with spontaneous epileptic seizures (Sirito *et al*., 1998). Similarly, rs29220 is a C10497G single base change in intron 9, the C allele is present in 20% of the TLE patients. *GABBR1* gene expression, quantified using RT-PCR, in sclerotic hippocampal tissue is influenced by genotype with impaired expression associated with the risk allele of both SNPs.

Gene expression data, although non-significant, when coupled with the genotyping analysis shows a clear trend in that $GABA_{B1}$ receptor expression is impaired in the presence of these SNPs, supporting the conclusion that they are involved in pathogenesis of TLE. In summary, we hypothesis that the promoter polymorphism rs29218 alters the binding of the transcription factor USF-1, which influences *GABBR1* expression, implicating a role for *GABBR1* in the pathogenesis of TLE.

Contact email address: b2006994@my.shu.ac.uk

Poster number: P-W130
Theme: Genetics & epigenetics

Investigating genetic variation in Alzheimer's disease using whole-exome sequencing

Authors: Tulsi Patel, Keeley Brookes, Tamar Guetta-Baranes, Sally Chappell - *Life Sciences University of Nottingham*, Paul Francis - *Wolfson Centre for Age Related Diseases King's College London*, Kevin Morgan - *Life Sciences University of Nottingham*

Alzheimer’s disease (AD) is an incurable neurodegenerative disorder; in which the death of brain cells characteristically result in memory loss and cognitive decline. It is the most common form of dementia, affecting around 850,000 people in the UK. The sporadic late-onset form (LOAD) accounts for 95% of all cases and is genetically complex in nature. It is believed that a combination of genetic and environmental factors are at play. Recent genome-wide association studies (GWAS) have uncovered 20 new gene candidates for AD risk, however these generally exhibit small effect sizes. Following on from GWAS, which addressed common variation associated with disease, we are now utilising whole exome next generation sequencing (NGS) to explore the contribution made by rare variants (MAF<5%). Recently this approach has highlighted the role of the TREM2, CD33 and SORL1 genes in AD risk and emerging NeuroX chip and NGS data is set to generate more genes of interest.

DNA was extracted from post-mortem brain tissue obtained from the BDR brain banks for healthy and diseased individuals. Whole-exome sequencing was performed on 292 samples, including 128 AD cases and 50 controls. Using a combination of bioinformatics and statistical tools we investigate how sequence variation, including deleterious mutations, within genes differs between a population of healthy and diseased individuals.

Using bioinformatic approaches, identified risk variants will be tested for association with disease. Pathogenic variants in known risk genes will be prioritised and their potential functionality assessed. A polygenic risk score (PRS) will be calculated for the individuals.

Presently over 340,000 variants have been identified in the whole-exome dataset. Variants in genes of interest that are annotated as highly damaging or protein modifying will be investigated further. Initial analysis revealed no mutations in the familial genes APP, PSEN1 or PSEN2. The generation of PRS will be a useful metric to inform individual’s level of risk for disease.

Contact email address: mbxtp1@nottingham.ac.uk

Poster number: P-W131
Theme: Developmental neuroscience

CHD7 controls cerebellar development via Reelin

Authors: Danielle Whittaker - *Clinical services The Royal Veterinary College*
Mutations in the gene encoding the ATP dependent chromatin-remodeling factor, CHD7 are the major cause of CHARGE (Coloboma, Heart defects, Atresia of the choanae, Retarded growth and development, Genital-urinary anomalies and Ear defects) syndrome. Neurodevelopmental defects in these patients lead to neurological dysfunction, including developmental delay, incoordination, intellectual disability and autistic traits. We previously demonstrated cerebellar vermis hypoplasia and abnormal cerebellar foliation in a proportion of patients with a CHD7 mutation and CHARGE syndrome. Abnormal foliation implicates CHD7 in perinatal cerebellar development, however its precise role is currently unclear.

We conditionally deleted Chd7 from granule cell precursors (GCps) in the mouse and identified cerebellar hypoplasia, purkinje cell disorganization, motor deficits and developmental delay in these mice. We found that Chd7 is critical in regulating granule cell proliferation and apoptosis in vivo. We report that Chd7 has a critical role in the regulation of Reln gene expression and identify a significant down regulation of Reln in GCps of the conditional Chd7 mutants by genome wide transcriptomic analysis and qPCR. We further provide functional evidence that Reln contributes to cerebellar hypoplasia in vivo, by demonstrating a partial rescue of central lobule hypoplasia in Chd7 mutants through the ectopic expression of Reln. Recessive mutations in RELN are associated with cerebellar hypoplasia and altered expression has been linked to a number of neuropsychiatric diseases. Through analysis of genome- wide chromatin accessibility we demonstrate that CHD7 is necessary to maintain an open, accessible chromatin state at the Reln locus and many other genomic regions. In conclusion, we show that CHD7 can be viewed as a previously unattributed upstream regulator of Reln, and that CHD7 dependent chromatin remodeling regulates Reln gene expression in the perinatal cerebellum. These data provide the first evidence of a direct in vivo role for a mammalian CHD protein in the regulation of cerebellar development through the modulation of chromatin accessibility in neuronal progenitors.

Contact email address: dwhittaker@rvc.ac.uk

Poster number: P-W132
Theme: Developmental neuroscience

Developmental profile of kainate-induced oscillations in layers II and V of the rat entorhinal cortex in vitro.

Authors: Emma Robson, Liselott Källsten, Naomi Culleton, Roland S. G. Jones - *Pharmacy and Pharmacology The University of Bath*
Neuronal network synchronisation within the gamma (30-80 Hz) frequency range is fundamental for a variety of cognitive and perceptual functions. In humans, gamma oscillations (GO) emerge during early childhood where they continue to mature until early adulthood, enabling coordination of spatially distributed neuronal activity. GO can be reliably replicated in vitro using kainic acid (KA) in the rat medial entorhinal cortex (MEC), an area associated with higher cognitive functions such as memory, spatial representation and navigation. However, the development of GO in the MEC has not been documented.

Here, we explored the developmental changes in kainate-induced oscillations (KA-O) in layers II (LII) and V (LV) MEC of Wistar rats at 5 ages (P8-11, P12-15, P16-19, P20-23 and P24-27) using local field potential recording in rat hippocampal-MEC slices. Measurements of peak amplitude and frequency were compared in the two layers.

KA-O were apparent at all ages and in both layers. However, an age dependent increase in amplitude was noted in L2 from 17.8±3.7 nV2/Hz in the youngest age group (P8-11; n=29) to a maximum average amplitude in group P20-23 (n=14) of 308.3±51.7 nV2/Hz ($P<0.001$). Unlike in L2, there was no age-dependent increase in amplitude in L5. Interestingly, in the youngest age group, the amplitude of L5 exceeded that of L2 (27/29 slices, $P=0.01$), a difference that was eliminated in the P12-15 group, and reversed in all slices thereafter (50/50 slices).

In both layers, there was a gradual increase in the peak frequency of KA-O from an initially low beta range of 18.1±0.4 Hz (L2) and 18.1±0.4 Hz (L5) in the youngest age group (n=29), attaining gamma frequency by P16-19 upwards, reaching a maximum of 31.3±0.7 Hz (L2) and 31.6±0.7 Hz (L5) in the oldest age group (P24-27; n=18, $P<0.001$). No differences in the average frequency were noted between the two layers.

These findings highlight clear laminar differences in the development of GO in the MEC. This has implications for understanding neuronal synchrony and normal development of cognitive function and spatial navigation behaviour and for neurodevelopmental disorders such as schizophrenia and epilepsy, which involve EC dysfunction.

Contact email address: er390@bath.ac.uk

Poster number: P-W133
Theme: Developmental neuroscience

New insights into the neurobiology of developmental dyslexia: the possible role of PCSK6 in driving hemispheric asymmetries in reading regions

Authors: Gloria Romagnoli - *Aston Brain Centre Aston University*

INTRODUCTION: Left-right asymmetry is an important organising feature of the human brain and has been found altered in neurocognitive disorders such as language impairments, schizophrenia and autism. Nevertheless, the underlying molecular mechanisms of such alterations are still almost completely unknown. A genome-wide association study revealed the association of the genetic variant rs11855415 in PCSK6 with relative handedness in individuals with dyslexia ($P < 10\text{-}7$) (Brandler et al. 2013). PCSK6 plays a key role in Left/Right patterning early in development via NODAL signalling and ciliogenesis, but we do not know yet how PCSK6 impacts on the brain.

OBJECTIVES: The purpose of this neuroimaging genetics study is to investigate the correlation between the genetic variant rs11855415 in PCSK6 and grey matter's total volume and distribution in dyslexic children, to find out whether this single-nucleotide polymorphism (SNP) is associated with altered hemispheric asymmetries in dyslexia.

METHODS: Dyslexic children between the ages of 7 and 16 were recruited for DNA collection and MRI scan. The subjects were stratified by genotype in two groups: (1) children without the minor rs11855415 allele (T/T); (2) children with the minor rs11855415 allele, in homozygosity (A/A) or heterozygosity (A/T). The subjects were matched by age, gender and handedness. The neuroimaging phenotypes of the two groups were compared by performing structural analysis on brain T1-weighted images. Tissue type segmentation, tissue volume quantification and voxel-based morphometry (VBM) analysis of grey matter were carried out by using the anatomical structure image analysis software FSL.

FINDINGS: The volumes of both grey matter and white matter have been found increased in the group carrying the SNP in comparison with the not carrier group. In the VBM analysis, the group without the SNP has shown a higher density of grey matter in the right inferior frontal gyrus (pars opercularis) than the carrier group.

CONCLUSIONS: These findings seem to be supportive of the hypothesis that PCSK6 might play a role in both driving altered hemispheric asymmetries and influencing traits such as reading ability.

Contact email address: gloria.neuroscience@gmail.com

Poster number: P-W134
Theme: Developmental neuroscience

How does sensory information interact with early interneuron circuits to direct the maturation of the neocortex?

Authors: Jacqueline Stacey, Simon J. B. Butt - *DPAG Oxford University*

Sensory activity plays an important role in the maturation of visual cortex (V1), in particular, ocular dominance plasticity. Similarly, in rodent somatosensory (S1BF) cortex, whisker input is required for barreloid development. These structural changes must be underpinned by changes on the circuit level. While the contribution of PV+ interneurons to cortical plasticity is well documented, less is known about the role of other interneuron (IN) subtypes.

Recently, we identified transient GABAergic input from L5b to L4 in the developing S1BF of the mouse. This connection consists of a reciprocal loop between L5b somatostatin-positive (SST+) INs to L4 spiny stellates that is only present prior to the end of L4 critical period (~P10). The presence and duration of this connection is modified by surgical perturbations to sensory input. Evidence suggests that this circuit is important for the timely acquisition of thalamic input onto L4 excitatory neurons. The extent to which sensory information influences remodelling of this circuit and whether this may be a general mechanism for sensory integration is unclear.

To address this we have mapped GABAergic connections onto L4 in a mouse devoid of any thalmo-cortical/cortico-thalamic connections. In the absence of thalamic input to the neocortex, the transient L5b onto L4 GABAergic connection is still present with the time course of this transient circuit un-altered. This suggests a possible genetic component to the formation and maintenance of this early IN-spiny stellate synapse. If this circuit is genetically hardwired to appear during development and is involved in correct integration of thalamic input, we might expect it to be present in other primary sensory areas. To investigate this we mapped GABAergic connections in the developing V1 to determine if similar connections exist between L5 INs and L4 pyramidal cells. Using laser scanning photostimulation we find no evidence of L5 GABAergic connections arising from SST+ INs onto L4 excitatory neurons in V1. This suggests that the connection between L5 SST+ INs and L4 excitatory neurons in S1BF is hardwired and area specific, highlighting a unique modality-specific role for SST+ INs in cortical development.

Contact email address: jacqueline.stacey@merton.ox.ac.uk

Poster number: P-W135
Theme: Developmental neuroscience

Early neurodevelopmental consequences of maternal immune activation at GD12.5 in Wistar rats

Authors: Joanna M Oladipo, Victoria Fasolino - *Division of Pharmacy and Optometry University of Manchester*, Michelle E Edye - *Neurorestoration Group King's College London*, Michael K Harte - *Division of Pharmacy and Optometry University of Manchester*, Jaleel A Miyan - *Division of Neuroscience & Experimental Psychology University of Manchester*, Joanna C Neill - *Division of Pharmacy and Optometry University of Mancheste*

Background: Viral infection in pregnancy has been associated with an increased risk for the development of autistic spectrum disorder (ASD). Maternal immune activation (mIA), using the viral mimetic poly(I:C), produces phenotypes relevant to ASD in rodents. mIA at gestational day (GD) 12.5 has been widely investigated in mice. However, no studies have explored mIA at GD12.5 in rats. Our aim is to characterise effects of mIA at GD12.5 on offspring neuro and gut biology and behaviour in Wistar rats.

Methods: Pregnant female Wistar rats were injected (i.p.) with poly(I:C) (10mg/kg, n=12 dams) or saline (n=14 dams) at GD12.5. Male and female offspring were monitored for changes in morphometric parameters at GD21, (body weight (BW), brain weight (BrW) and placental weight (PW) n=6 dams/treatment). BW was measured postnatally, and on postnatal day (PD) 21 BrW was measured (n=6-8 dams/treatment). Gene expression in frontal cortex of GD21 offspring was measured using qPCR. For data analysis between treatment groups, a nested-ANOVA was used with litter as a random variable.

Results: At GD21 no significant effect of mIA was observed on BW or BrW in either sex. A significant reduction was found in the PW of female poly(I:C) offspring ($p<0.01$). Gene expression analysis revealed a significant increase in microglial marker Ofml3 in frontal cortex of male poly(I:C) offspring ($p<0.01$). Postnatally, a significant reduction in BW was found at PD1 in both sexes from poly(I:C) dams vs. saline ($p<0.001$). This reduction was maintained at PD12, 18 and 21 ($p<0.001$). When normalised to BW, BrW from offspring at PD21 was increased in offspring from poly(I:C) dams vs. saline (male $p<0.01$ female, $p<0.001$).

Conclusion: To our knowledge this is the first mIA study investigating the effects of 10mg/kg poly(I:C) in Wistar rats at GD12.5. We provide an in depth early developmental analysis of both male and female offspring in this model. mIA resulted in increased frontal cortex gene expression for microglia in male offspring at GD21. An increase in BrW at PD21 may indicate reduced synaptic pruning during development. Further validation of this model is underway to explore effects on gene expression related to synaptic pruning and other brain markers relevant to ASD at PD21.

Contact email address: joanna.dennison@postgrad.manchester.ac.uk

Poster number: P-W136
Theme: Developmental neuroscience

Opiate exposure during early neonatal life has long term effects on breathing pattern

Authors: Leanne McKay - *Institute of Neuroscience and Psychology University of Glasgow*

The mammalian respiratory system is immature at birth. In mice, this immaturity is characterized by a fragile and highly variable breathing pattern during postnatal days 1-3 (P1-3). Around P3-P4, the respiratory system undergoes a step in maturity, after which breathing is less variable and has a higher frequency. The neural mechanisms underlying this maturation step are unknown. Evidence from in vitro studies suggests that two distinct medullary neuronal clusters, the opiate sensitive preBötC and the opiate-insensitive RTN/pFRG, play a critical role in generating respiratory rhythm but little is known of their interaction during development and early post-natal life when the respiratory system is fragile. To pharmacologically tease apart the function of these neuronal clusters during early postnatal maturation of breathing and to investigate the long term effects of opiates on breathing pattern, neonatal mice were exposed to the μ-opioid receptor agonist fentanyl (0.08mg/kg i.p daily), or saline as a control, from P1-5 (n=16) or P9-13 (n=16). Mice were continuously monitored post injection and breathing recorded by closed plethysmography at regular intervals from 5 minutes to 2 hours post injection.

Fentanyl had a modest effect on breathing at all postnatal days by increasing variability, decreasing frequency and increasing the number of apnoeas and hyperpnoeas, compared to saline-exposed mice. At 6 weeks of age, all saline and fentanyl exposed mice were exposed to a single dose of fentanyl (0.04 – 1.0mg/kg ip) and monitored as above. Post-fentanyl, respiratory frequency was significantly decreased (190±10 vs120±15 breaths per minute) in all mice previously exposed to saline as neonates (P1-P5 and P9-13); however, in mice previously exposed to fentanyl as neonates (P1-P5 and P9-13), exposure to a single injection of fentanyl in adulthood had no effect on respiratory frequency (180±8 vs 150±10 bpm). Tidal volume increased slightly in all mice post fentanyl regardless of previous exposure to fentanyl or saline. These data suggest that the respiratory system in younger animals is less susceptible to fentanyl and that pre-exposure to fentanyl during early post-natal maturation brings about a desensitization to fentanyl during wakefulness in early adulthood.

Contact email address: leanne.mckay@glasgow.ac.uk

Poster number: P-W137
Theme: Developmental neuroscience

Cortical sources of spontaneous alpha during adolescence: Relationship with puberty and gender but not risk taking

Authors: Liat Levita, Philippa Howsley - *Psychology University of Sheffield*

This study aimed to investigate how the cortical sources of spontaneous alpha during eyes-open and eyes-closed conditions change during the course of adolescence as a function of age and pubertal stage. In addition, with regards to spontaneous alpha there is a long-standing theory suggesting that relatively greater left frontal cortical activity is associated with reward orientated behaviours and relatively greater right frontal neural activity is associated with avoidance-orientated behaviours, as indexed by spontaneous EEG alpha activity (Davidson, 1984, 1994). While there is evidence for this theory in adults, research examining frontal asymmetry and its relationship to risk-taking in adolescents is limited. Hence, the aim of this study was to examine whether frontal asymmetry could account for the developmental differences in risk-taking behaviours in adolescents. To that end, preadolescents (9-12 years), mid-adolescents (13-17 years), and late adolescents (18-23 years) had their resting brain activity measured using EEG during eyes open and eyes-closed conditions. The findings revealed significant changes during the course of adolescence, with an age-dependent reduction in occipital alpha in the eyes closed condition, and shift in prefrontal cortical sources of alpha during the eyes-open condition. In addition, more advanced pubertal development was found to predict reduced alpha activity in male, but not female, adolescents. Unexpectedly, frontal asymmetry was found not to be a reliable marker of risk-taking behaviours. In conclusion, this study provides an important step towards understanding the development of spontaneous alpha in the typically developing brain. Nonetheless, a great deal more research needs to be conducted before we have a complete understanding of the development and functional significance of alpha in the maturing brain.

Contact email address: l.levita@sheffield.ac.uk

Poster number: P-W138
Theme: Developmental neuroscience

Role of Supraspinal Dopaminergic Neurons in Regulating Maturation of Zebrafish Behaviour

Authors: Raad O. Ramadhan, Jonathan R. McDearmid - *Department of Neuroscience, Psychology and Behaviour University of Leicester*

Dopamine (DA) is a key neuromodulator of the adult nervous system. In addition, recent evidence suggests that DA also has neurodevelopmental roles, although these have yet to be fully defined. To address this problem, we are using early stage zebrafish to investigate DAergic regulation of motor behaviour. To determine when spinally projecting DAergic neurons first innervate the spinal cord, we used anti-tyrosine hydroxylase immunohistochemistry. We find that by 22 hours post fertilisation (hpf), DAergic axons reach the caudal part of the hindbrain, reaching the rostral most aspect of the spinal cord shortly afterwards at 24 hpf. Thereafter, DAergic axons gradually extend to more posterior compartments of the spinal cord. To investigate the role of DA signalling on the maturation of zebrafish motor behaviour I used pharmacology and laser ablation methods to study the effects of DA disruption on coiling, a simple form of motor behaviour that is transiently expressed when DAergic axons first invade the spinal cord. Subsequent behavioural and patch clamp analysis revealed that blocking of DA signalling increases the frequency of coiling behaviour and the periodic depolarisations that underpin them while DA receptor agonists has the opposite effect. Therefore, during early stages of development DAergic signalling may promote the termination of transient forms of immature motor behaviour and permit the transition to more complex forms of motor output.

Contact email address: ror3@le.ac.uk

Poster number: P-W139
Theme: Developmental neuroscience

Mechanistic investigation of AhR pathway contribution to medulloblastoma tumorigenesis

Authors: Saric N, Pijuan Sala B, Hogstrand C, Basson MA. - *Craniofacial Development and Stem Cell Biology King's College London*

Gestational exposure to environmental toxicants can adversely affect postnatal and adult development. Neurotoxicology data suggests that certain environmental toxicants (such as the compound TCDD) have a potent effect on cerebral development, through pro-apoptotic effects on cerebellar granule cells (MA Williamson, 2005 ToxSci; LL Collins, 2008 ToxSci), defects in pituitary activity (Takeda T et al, 2011 Tox Sci), defects in brain vasculature (Teraoka H et al 2010) as well as alterations in hippocampal neurogenesis and function (Opanashuk et al, 2013 J Neurochem).The major pathway through which TCDD signals is the aryl hydrocarbon receptor (AhR) pathway, whereby the ligand-activated transcription factor AhR binds to associated nuclear translocator proteins (ARNT/ARNT2), is transported through the nuclear membrane and evokes its downstream effects through binding to XRE sequences in the genome. This signalling axis is regulated via negative feedback by AhRR (aryl hydrocarbon receptor repressor). In the context of certain complex disorders, such as cancers, the epigenetic mechanisms as well as the conclusive role of environmental factors contributing to disorder aetiology remain to be elucidated.

The focus of this research is whether aberrant AhR pathway signalling in the developing cerebellum contributes to medulloblastoma tumorigenesis in murine models. To achieve this, we have utilized double conditional Ptch1 (Patched1)/AhR and AhRR mutants, which have allowed us to model the Shh subclass medulloblastomas and pose the question of whether key AhR pathway components are able to influence the process of medulloblastoma development, and if so, through what mechanisms. Our data from non-neoplastic cerebellar granule precursors (GCPs) suggest a role for the AhR in maintenance of GCP cycling throughout the early postnatal time period of cerebellar neurogenesis via repression of the Tgf beta pathway, specifically through inhibiting phosphorylation of Smad3. The pathological medulloblastoma context, we hypothesize, may involve a role reversal for the AhR, with loss of function leading to enhanced tumorigenesis. Along with key data pertaining to AhRR function this study aims to provide a more thorough mechanistic understanding of the AhR pathway in medulloblastoma.

Contact email address: nemanja.saric@kcl.ac.uk

Poster number: P-W140
Theme: Developmental neuroscience

Can a neurological representation of pain-related brain activity be defined using fMRI in infants?

Authors: Sezgi Goksan, Luke Baxter - *Department of Paediatrics University of Oxfor*d, Eugene Duff - *Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) University of Oxford*, Caroline Hartley, Rebeccah Slater - *Department of Paediatrics University of Oxford*

Background: In infants, reliance on surrogate pain-related measures is essential for pain assessment. As cortical activation is a pre-requisite for pain perception, inferences based on brain activity patterns may provide the most reliable surrogate measures. Acute mildly noxious stimulation generates a widespread pattern of brain activity in newborn infants, which is similar to that observed in adults [1]. We want to establish whether it is possible to refine and test a template of pain-related brain activity in infants.
Methods: 21 newborn infants had structural and functional magnetic resonance images (fMRI) collected at the Oxford Centre for Functional MRI of the Brain (FMRIB), John Radcliffe Hospital. All infants were between 1 and 11 days old at the time of the study (gestational age at study: 35 - 43 weeks).

T2-weighted turbo spin echo structural and functional echo planar imaging scans were acquired in all infants at 3T. During the functional scans, a 64 mN and 128 mN mildly noxious force was applied to the left foot.
All data were collected and pre-processed as described in Goksan et al. 2015 [1]. A template of pain-related brain activity, developed for use in adults [2], was registered to a group structural image of an infant's brain at 40-weeks gestation [3]. The template was then applied to each individual subject's functional data.

Results: The template was able to discriminate between pain and no-pain trials, and predict stimulus intensity with approximately 80 % sensitivity. 17 of the 21 infants had a response characterised by the template that was greater following the 128 mN force as compared with 64 mN force.
Conclusions: A template of pain-related brain activity, that was initially developed in adults, has been adapted for use in infants, and can discriminate between different intensities of noxious-evoked brain activity. A machine-learning approach can be applied to infant fMRI data to refine and test this template, which may provide a sensitive tool for identifying pain in individual infants and for assessing analgesic efficacy.

1. Goksan, S et al. eLife 2015.
2. Duff, E P et al. Sci Transl Med 2015.
3. Serag, A et al. NeuroImage 2012.

Contact email address: sezgi.goksan@paediatrics.ox.ac.uk

Poster number: P-W141
Theme: Developmental neuroscience

Excitatory Cortical Connectivity is Biased by Progenitor Cell Identity

Authors: Sophie Avery - *Department of Pharmacology University of Oxford*

A fundamental question in neuroscience is how neurons establish their functional identity and what instructs them to make specific synaptic connections with other neurons. One hypothesis is that these properties are determined by the developmental origins of the neurons. Our work builds upon the observation that excitatory cortical neurons are generated from a heterogeneous pool of neural progenitors located within the ventricular zones of the embryonic brain. Short Neural Precursors, SNPs, have been shown to represent a distinct population of cortical progenitors, which can be distinguished from other progenitors based on their cell cycle kinetics, gene expression profile and morphology.

Using the somatosensory cortex of the mouse as a model system, we have investigated the extent to which SNPs may influence the functional identity and connectivity profiles of the excitatory pyramidal neurons that they generate. This was achieved by labelling SNP and non-SNP derived neurons using a differential fluorophore expression technique. Our data show that while SNP and non-SNP derived pyramidal neurons in layer II/III have similar intrinsic electrophysiological properties, they differ in their long-range input from the thalamus, and their translaminar output to layer V. Specifically, SNP-derived neurons preferentially receive input from the posterior medial (POm) nucleus of the thalamus, while non-SNP derived neurons preferentially receive input from the ventral posterior medial (VPM) nucleus. With respect to translaminar output, SNP-derived neurons preferentially drive activity in layer Va pyramidal neurons, whilst non-SNP derived neurons preferentially drive layer Vb pyramidal neurons. This work uncovers a novel influence of neuronal lineage upon mature neuronal connectivity within the cortex.

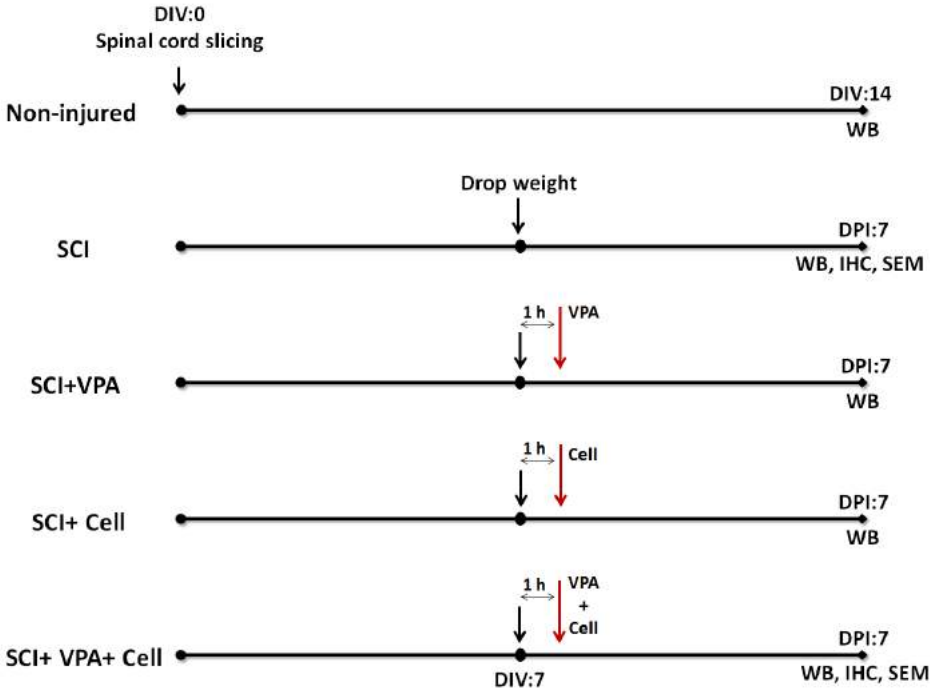
Contact email address: sophie.avery@balliol.ox.ac.uk

Poster number: P-W142
Theme: Developmental neuroscience

Evaluation of epidermal neural crest stem cells in the injured organotypic spinal cord slice culture

Authors: Sareh Pandamooz - *Department of Animal Biology Kharazmi University*, Leila Dargahi - *Neuroscience Research Center Shahid Beheshti University of Medical Sciences*, Mohammad Nabiuni - *Department of Animal Biology Kharazmi University*

Spinal cord injury (SCI) is a devastating condition causing long lasting consequences. Among various therapeutic strategies employed for SCI, stem cell therapy is a potential treatment. By far variety of stem cells have been evaluated which epidermal neural crest stem cells (EPI-NCSCs) is one of the attractive types. Although these multipotent stem cells have been assessed in several SCI models, so many works remain to be done to clarify all aspects of its therapeutic effects. Here, EPI-NCSCs in combination with valproic acid (VPA), a well-known histone deacetylase inhibitor was evaluated in ex vivo model of injury. To do so, the contusion was stimulated in organotypic spinal cord slice cultures. Subsequently, 5 µM VPA was administered to the injured slices one hour after injury. Then, green fluorescent protein- expressing EPI-NCSCs were grafted following treatment with the VPA. The treated slices were assessed with immunohistochemistry and immunoblotting seven days after transplantation. Obtained data revealed that grafted stem cells can survive on the injured slices and express GFAP- traditional astrocyte marker- while did not express any detectable level of doublecortin- neural progenitor marker- which was common marker ahead of transplantation. Also immunoblotting revealed significant increased expression of GFAP, BDNF, NT-3 (neurotrophin-3) and Bcl2 in injured slices treated with stem cells alone or combination of stem cells and VPA. This study illustrated that EPI-NCSCs transplantation in the ex vivo model of injury can increase neurotrophic and neuroprotective factors which in turn may provide a hospitable context and contribute to promotion of axonal regeneration.



Contact email address: sareh_158@yahoo.com

Poster number: P-W143
Theme: Neuroendocrine & autonomic systems

The acute effects of non-invasive trigeminal nerve stimulation on cardiovascular autonomic function

Authors: Aaron Murray - *School of Biomedical Sciences University of Leeds*, Jennifer Clancy - *School of Life Sciences University of Glasgow*, Susan Deuchars, Jim Deuchars - *School of Biomedical Sciences University of Leeds*

Non-invasive trigeminal nerve stimulation (TNS) is under investigation as an adjunctive neuromodulation therapy for treatment-resistant epilepsy and treatment-resistant major depressive disorder. The mechanism of action of TNS is unclear but the nucleus

tractus solitarius (NTS), a key brainstem region associated with cardiovascular autonomic control, is known to receive trigeminal inputs. The present study investigated the potential acute effects of TNS on cardiovascular autonomic function in healthy human volunteers.

27 volunteers (16 female, 11 male; age range 21-59 years) attended two separate visits at least one week apart to receive either high frequency TNS (H-TNS; 120Hz, 250µs) or low frequency TNS (L-TNS; 30Hz, 200µs). Stimulation was applied for 15 minutes to the supraorbital region using transcutaneous electrical nerve stimulation (TENS). Ten volunteers returned for a further visit where a sham protocol (sham-TNS) was performed. Heart rate, blood pressure and respiration were recorded at baseline, during stimulation and after stimulation. Heart rate variability (HRV) was calculated from power spectral analysis of beat-to-beat oscillations in heart rate. The LF/HF ratio was calculated using low frequency power (LF power; 0.04-0.15Hz) and high frequency power (HF power; 0.15-0.4Hz).

No changes in LF/HF ratio were observed for any of the three stimulation parameters. Female participants had a reduction in HF power ($p<0.05$) during H-TNS but this reduction was not detected during L-TNS or sham-TNS. Male participants experienced a slight decrease in mean heart rate from baseline during L-TNS ($p<0.05$), but there was no concurrent change in HRV. Female participants experienced a slight decrease in heart rate after L-TNS and H-TNS had ceased ($p<0.05$) but did not experience a decrease during stimulation. No changes in blood pressure or respiration rate were observed as a result of TNS.

These preliminary results indicate that TNS may have no overall acute effect on cardiovascular autonomic function in healthy human volunteers. Further studies are needed to assess the cardiovascular and autonomic effects of chronic TNS in both healthy volunteers and clinical populations with neurological or psychiatric disease.

Contact email address: bsarm@leeds.ac.uk

Poster number: P-W144
Theme: Neuroendocrine & autonomic systems

Diurnal signaling of retinoic acid in the rat pineal gland and its role in the regulation of kinase activity.

Authors: Anna Ashton, Patrick Stoney, Peter McCaffery - *Institute of Medical Sciences University of Aberdeen*

The pineal gland is an integral component of the circadian timing system due to its role in producing the nocturnal hormone melatonin. Previous studies have alluded to an important role for vitamin A (retinol) in this gland. Vitamin A deficiency has been shown to lead to a disappearance in the daily rhythm in MAPK activation, as a well as a reduction in the night-time peak in melatonin (1, 2). Retinol primarily acts through its active metabolites, retinal and retinoic acid (RA). Previous studies have shown that retinal is absent from the pineal gland, suggesting the effects of retinol are mediated by RA. RA is a potent regulator of gene transcription and has been shown to have non-genomic activities including activation of kinases. The overall aim of this study was to investigate whether the RA signaling system is present in the rat pineal gland and whether it exhibits a daily rhythm in activity. The study also investigated whether RA regulates kinase activity in the pineal gland, including ERK1/2 and p38 MAPK. The presence of RA signaling components in Sprague Dawley rat pineal glands was investigated by PCR and western blotting. Sprague Dawley rat pineal glands were then collected at six hour intervals and analysed by qPCR to determine the expression of RA signaling components throughout the light/dark cycle. Organotypic culture of rat pineal glands together with qPCR and western blotting were used to study the effect of RA on expression of RA-responsive genes and kinase activation, respectively. RA receptors and key synthetic enzymes were found to be present, some of which were shown to exhibit day/night changes in expression. One of these, the RA-responsive gene Cyp26a1, was found to be rapidly upregulated by RA in cultured pineal glands, suggesting it may be used as an indicator of RA activity. Together these results suggest that there are diurnal changes in RA activity in the rat pineal gland. This study identifies a new rhythmic signaling system in the mammalian pineal gland which may have a role in driving diurnal changes in kinase activation and gene expression.

1. Guillaumond F et al. (2005) Eur J Neurosci. 21, 798-802.
2. Herbert DC & Reiter RJ (1985) Life Sci. 37, 2515-22.

Contact email address: a.ashton@abdn.ac.uk

Poster number: P-W145
Theme: Neuroendocrine & autonomic systems

Chronic synthetic glucocorticoid treatment alters the activity balance between glucocorticoid and mineralocorticoid receptors in the hippocampus

Authors: Emma Victoria Earl, Stafford L. Lightman, Becky L. Conway-Campbell - *School of Clinical Sciences University of Bristo*
Synthetic glucocorticoids (sGC) are widely used in the clinic due to their potent anti-inflammatory properties, however some patients exhibit adverse side effects including behavioural, affective and cognitive dysfunction. The sGC dexamethasone (Dex) is a potent and selective glucocorticoid receptor (GR) agonist, with an extremely low affinity for the mineralocorticoid receptor (MR). In contrast, endogenous glucocorticoids including cortisol and corticosterone are mixed agonists, with a high affinity for MR and a low affinity for GR. In the hippocampus, both MR and GR are highly expressed and the balance between the two receptors is thought to play a crucial role in homeostatic mechanisms, stress responses, and memory and learning processes. Therefore, here we have assessed the effects of chronic Dex treatment on the GR/MR ratio in the hippocampus.

Male Lister-Hooded rats were treated for five days with 12 hourly subcutaneous Dex injections (1mg/kg) then killed 1 hour after the final injection at either 8PM or 8AM, corresponding to the circadian peak and nadir respectively. Results from in situ hybridization immunohistochemistry studies show suppressed CRH expression in the hypothalamic paraventricular nucleus (PVN), consistent with chronic central GR activation. Consistent with increased negative feedback throughout the hypothalamic-pituitary-adrenal (HPA) axis, adrenal corticosterone secretion was suppressed to undetectable levels. Hippocampal GR protein levels were also downregulated, due to an autoregulation mechanism. Despite lower total protein levels, there was a notable increase in GR protein in the active nuclear fraction in both the AM/PM, consistent with Dex-induced 'hyperactive' GR activation during both the circadian nadir and peak. In contrast, MR activation was significantly decreased, as would be expected with suppression of its endogenous ligand. Therefore, this combination of GR 'hyper-activation' and MR 'hypo-activation' may contribute to the development of adverse behavioural, cognitive and affective state symptoms in susceptible individuals treated with sGCs. Our results highlight the importance of considering both pharmacodynamics and chronobiology when treating patients with GCs in the clinic.

Contact email address: a emma.earl@bristol.ac.uk

Poster number: P-W146
Theme: Neuroendocrine & autonomic systems

Bitter taste receptor mediated Ca2+ signalling in hypothalamic tanycytes

Authors: Eric Pollatzek, Nicholas Dale - *School of Life Sciences University of Warwick*

Hypothalamic tanycytes are glial-like cells that contact cerebrospinal fluid of the 3rd ventricle, and send long processes into the brain parenchyma of hypothalamic arcuate nucleus (ARC) and the ventromedial hypothalamic nuclei (VMH). The ARC and VMH are accessible to circulating hormones such as leptin or insulin and metabolites such as glucose, free fatty acids or amino acids. These nuclei integrate this information to regulate food intake, food preference and bodyweight.

We have recently shown that tanycytes respond to glucose and amino acids via a variety of receptors, which include members of the Tas1r gene family. The aim of this study was therefore to test whether members of the Tas2r gene family that encode a series of bitter taste receptors might also be functionally expressed in hypothalamic tanycytes.

We used acute hypothalamic slices prepared from C57/BL6 mice in which tanycytes had been loaded with Fura-2 to measure intracellular Ca2+. Selective stimulation of tanycyte cell bodies by bitter tasting compounds (such as L-Phe, L-Trp, strychnine emetine and quinine) evoked robust Ca2+ responses in tanycytes. The agonist profile of the evoked responses is consistent with the presence of Tas2r108 and Tas2r140 in tanycytes and excludes the presence of Tas2r105, Tas2r110, Tas2r119 and Tas2r144.

We propose that tanycytes use members of the Tas2r gene family to sense bitter tasting essential amino acids, such as phenylalanine and tryptophan in the cerebrospinal fluid.

Contact email address: E.pollatzek@warwick.ac.uk

Poster number: P-W147
Theme: Neuroendocrine & autonomic systems

Immune stress-induced disruption of glucocorticoid-mediated intra-adrenal negative feedback leads to elevated glucocorticoids secretion in the rat

Authors: Francesca Spiga - *School of Clinical Sciences University of Bristol*

In basal conditions ultradian rhythm of glucocorticoid hormones depends on pulsatile secretion of ACTH. We have recently shown that ACTH and cortisol dissociation occurs in patients undergoing cardiac surgery, with high levels of cortisol despite normal levels of ACTH. We have also shown the acute administration of lipopolysaccharide (LPS) results in a similar dissociation between ACTH and corticosterone in the rat, and this is associated with a increase of StAR mRNA and a decrease of DAX-1 mRNA expression in the adrenal gland. In this study we further investigated the dynamic activity of the adrenocortical steroidogenic pathway in response to LPS in the rat, and to better elucidate the specific role of inflammatory mediators, the effects of LPS were compared to these induced by a high dose of ACTH.

Male adult rats were injected with LPS (100 ng/i.v.) or ACTH DEPOT (2 ug/kg; s.c.).Trunk blood and adrenal glands were collected at specific time point prior to and following each treatment. Plasma levels of ACTH and corticosterone were measured using Radioimmunoassay; Transcriptional activity of steroidogenic genes in the adrenal was investigated by measuring hnRNA and mRNA by RTqPCR; Steroidogenic protein expression and activity was measured using Western blotting.

While administration of ACTH induced a rapid and transient effect on both ACTH and corticosterone, in LPS-treated rats corticosterone remained high after plasma ACTH returned to basal. These effects were associated with a more prolonged increase in pHSL-Ser660 -but not pHSLSer563, in LPS-treated rats, compared to ACTH-treated rats.

Furthermore, differences between ACTH and LPS treatment were also observed in the dynamics of the steroidogenic pathway regulating steroidogenic protein expression, including a more robust increase in newly synthetized StAR and a biphasic effect on DAX-1 expression in LPS-treated rats. Remarkably, these affects were not associated with any increase in glucocorticoid receptor phosphorylation. Our data show that inflammatory mediators can affect dynamic of the steroidogenic pathway in vivo in the adrenal of rat and suggests novel mechanisms through which ACTH and glucocorticoids dissociation occurs during inflammation. Importantly, our data are consistent with our recent

Contact email address: f.spiga@bristol.ac.uk

Poster number: P-W148
Theme: Neuroendocrine & autonomic systems

Multiple mechanisms of amino acid sensing in hypothalamic tancycytes

Authors: Greta Lazutkaite, Nicholas Dale - *School of Life Sciences University of Warwick*

Hypothalamic tanycytes are glial cells that line the third ventricle of the hypothalamus and send processes into other areas of the hypothalamus involved in appetite control. They monitor the concentration of nutrients such as glucose and amino acids in the cerebrospinal fluid composition. Our aim is to identify the mechanisms by which tanycytes detect amino acids.
We used Ca^{2+} imaging in hypothalamic mouse and rat brain slices to show that amino acids activate tanycytes via both the Tas1r1/Tas1r3 heterodimer and mGluR4. These two receptors are known to be involved in rodent and human umami (savoury) taste detection in taste buds. Tests in Tas1r1-KO mice revealed sexual dimorphism: in the female KO group, tanycyte responses to L-arginine and L-lysine, but not L-alanine, were reduced (median $\Delta F_{340}/F_{380}$ Arg WT 0.292 vs KO 0.047, Lys WT 0.125 vs KO 0.045, Ala WT 0.048 vs KO 0.038). No such effects were observed in males. However, blocking mGluR4 with a selective antagonist MAP4 in WT males partially reduced the responses to L-lysine and eliminated the responses to L-alanine (median $\Delta F_{340}/F_{380}$ Lys control 0.157 vs MAP4 0.081, Ala control 0.041 vs MAP4 0.015). These data suggest that both mGluR4 and Tas1r1/Tas1r3 are necessary for tanycyte amino acid sensing. mGluR4 could act as a compensatory mechanism where Tas1r1/Tas1r3 is lost and this may be more effective in males than females.

This is, to date, the first known non-neuronal mechanism of direct amino acid sensing in the brain. As amino acids are a powerful signal of satiety, our discovery may facilitate new mechanistic approaches to the treatment and prevention of obesity and other metabolic disorders.

Contact email address: g.lazutkaite@warwick.ac.uk

Poster number: P-W149
Theme: Neuroendocrine & autonomic systems

High frequency pelvic nerve stimulation to modulate urinary continence – a proof of concept study in conscious rats

Authors: Jonathan Crook, Charly Brouillard - *Physiology Pharmacology and Neuroscience University of Bristol*, Kelsey Bayer, Jay Shah, Pedro Irazoqui - *Weldon School of Biomedical Engineering Purdue University*, Thelma Lovick - *Physiology Pharmacology and Neuroscience University of Bristol*

We have shown in urethane-anaesthetised rats that 1-3kHz stimulation of the pelvic nerve inhibits urinary voiding(1). This finding raised the possibility of developing pelvic nerve stimulation as a novel approach to manage urinary voiding dysfunction in humans.

Pelvic nerve stimulation in freely moving rats has not previously been reported. As the first step towards assessing its translational potential we investigated how rats tolerated electrodes chronically implanted on the pelvic nerve, and their responses to high frequency stimulation. In 5 female Wistar rats a bipolar stimulating cuff electrode (Pt/Ir wire with cobalt core embedded in a silicone cuff) was implanted onto the left preganglionic pelvic nerve under isofluorane anaesthesia. Leads were tunneled subcutaneously and exteriorized via a connector embedded in dental acrylic anchored to the skull via 4 stainless steel screws.

The rats showed a normal diurnal voiding pattern in a metabolic cage 5-7 days post-operatively, i.e. smaller, more frequent voiding in the dark period (16.00-04.00h). Compared to the previous hour (baseline), pelvic nerve stimulation (30-60min, 1-3kHz, sinusoidal 0.125-4mA during the dark period) evoked a change in pattern to smaller, more frequent voids but no change in voided volume (median 2.0 v. 1.3ml/h, $p>0.05$ Dunn's post-hoc test). On cessation of stimulation, the volume voided in the next hour was reduced compared to baseline (median 0.7 v. 1.3ml/h $p<0.05$). This effect was not secondary to a change in time asleep. Comparable changes were seen when rats were re-tested 2-4 days later. In terminal experiments 19-21 days post implantation, high frequency stimulation (1-3kHz, 0.25-4mA) evoked only a brief (3.3-15.5s) rise in bladder pressure (an 'on response'), whilst low frequency stimulation (10Hz, 0.1-5mA for 10s) evoked an intensity-related increase in pressure.

The results indicate that 1) chronic implantation of electrodes on the pelvic nerve for 3 weeks does not compromise the normal pattern of voiding 2) high frequency pelvic nerve stimulation is well tolerated, 3) high frequency pelvic nerve stimulation can modulate urinary voiding in a reversible and reproducible manner.

Supported by MRC, GSK & IMPRESS
1) Crook JJ, Lovick TA (2016) Proc Physiol Soc 36 184P

Contact email address: jon.crook@bristol.ac.uk

Poster number: P-W150
Theme: Neuroendocrine & autonomic systems

Selective inhibition of FKBP51 alters ultradian and stress-induced corticosterone secretion in the rat

Authors: Julia Gjerstad, Zidong Zhao - *School of Clinical Sciences University of Bristol*, Xixi Feng, Felix Hausch - *Institute of Psychiatry Max Planck*, Stafford Lightman, Francesca Spiga - *School of Clinical Sciences University of Bristol*

The hypothalamic-pituitary-adrenal (HPA) axis regulates the release of glucocorticoids (CORT). CORT secretion is characterised by both circadian and ultradian rhythms which are strongly affected by age, gender, and disease states in the rat. The FK506 binding protein 51 (FKBP51) regulates the effects of glucocorticoids by inhibiting nuclear translocation of the glucocorticoid receptor (GR) and affects the negative feedback of CORT release. In humans, polymorphism and overexpression of the FKBP51 gene is associated with elevated levels of CORT, linked to mental disorders including anxiety and depression. To further investigate the role of GR and FKBP51 in regulating ultradian rhythm of CORT, we used the recently developed FKBP51-specific antagonists SAFit2 (central and peripheral effects) and SAFit1 (peripheral effects only). Adult male Sprague-Dawley were given acute treatment of SAFit2 (20mg/kg, 09.00h and 17.00h, SC) or SAFit1 (20mg/kg, 09.00h, 14.00h and 19.00h, SC). The ultradian rhythmicity of CORT was assessed using an automated blood-sampling system, collecting blood every 10 minutes for 24 hours. A noise stress was used to investigate the effects of SAFit2 and SAFit1 on stress-induced CORT secretion. Plasma CORT was measured in the blood samples using radioimmunoassay. SAFit2 decreased both stress-induced and basal CORT secretion, suggesting that inhibition of central (and

peripheral) FKBP51 increase GR-mediated negative feedback. This supports previous studies in our lab indicating that ultradian CORT rhythm is generated and maintained by a positive feedforward- negative feedback interaction between the anterior pituitary and the adrenal gland. In contrast, SAFit1 significantly increased basal CORT levels but had no effect on the stress-induced CORT response. This suggests a central regulation of the stress-induced negative feedback, whereas the mechanisms underlying the enhancing effect of SAFit1 on basal CORT are not yet clear. Ongoing sub-chronic and molecular studies will help elucidate the mechanisms behind these effects. Overall, our data provide insights into the regulation of ultradian rhythmicity, and show that inhibition of central FKBP51 may represent a novel therapeutic approach for disorders associated with increased HPA axis activity.

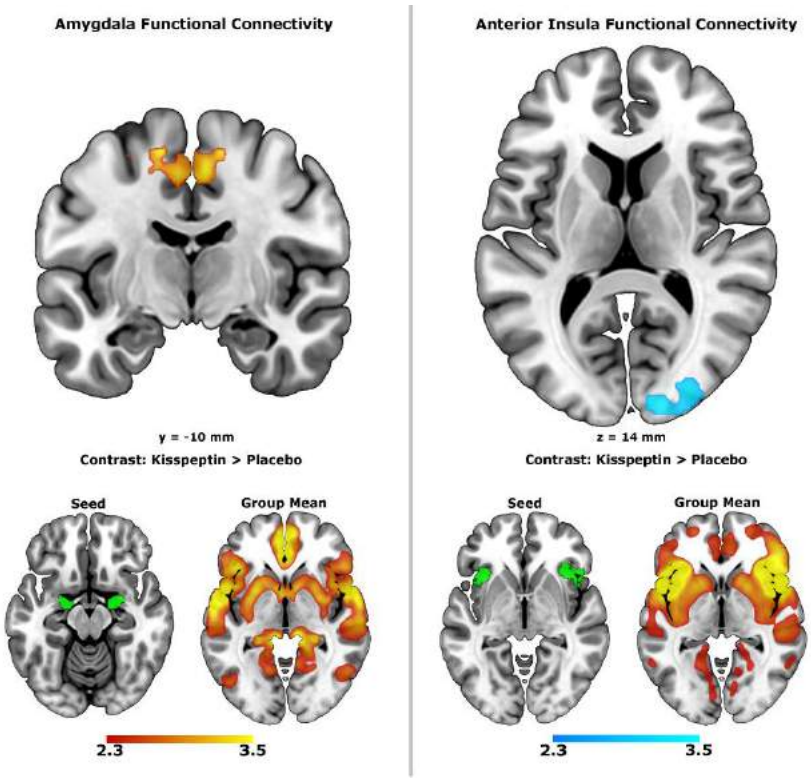
Contact email address: jg14339@bristol.ac.uk

Poster number: P-W151
Theme: Neuroendocrine & autonomic systems

The effects of the novel sex hormone kisspeptin on resting state functional connectivity

Authors: Lysia Demetriou - *Department of Medicine Imperial College London*, Alexander Comninos - *Investigative Medicine Imperial College London*, John McGonigle - *Image Analysis Imanova*, Matt Wall - *Clinical Applications Imanova*, Amar Shah, Sophie Clarke, Shakunthala Narayanaswamy, Alexander Nesbitt, Chioma Izzi-Engbeaya, Julia Prague, Ali Abbara, Risheka Ratnasabapathy, Victoria Salem, Monica Nijher - *Investigative Medicine Imperial College London*, Mark Tanner, Eugenii Rabiner - *Clinical Applications Imanova*, Steve Bloom, Waljit Dhillo - *Investigative Medicine Imperial College London*

Kisspeptin is a crucial activator of reproductive function. It plays a role in the hypothalamus to activate GnRH neurons and downstream reproductive hormones, and its receptor is also expressed in limbic brain areas. Kisspeptin signalling in the amygdala modulates neural activity and reproductive hormone secretion in rodents and humans. Comninos et al. [1] demonstrated that kisspeptin modulates limbic brain activity in men in response to sexual and emotional stimuli. Here we explore the effects of kisspeptin administration by examining resting state networks (Default (DMN)/Executive, Salience, and amygdala networks), MRI data were acquired for 29 healthy men (mean age 25.4) on a Siemens 3T Trio scanner within a randomized blinded two-way placebo-controlled protocol. Participants received a 75 minute infusion of 1 nmol/kg/h kisspeptin-54 to provide steady-state levels of circulating kisspeptin. A resting state eyes-open scan was acquired 1 hour post infusion start. Imaging parameters included: EPI 36 slices, 3x3x3mm voxels, TE=31 ms, TR =2000ms. Data was processed using AFNI, FreeSurfer, ANTs, and FSL, following the method used in [2]. This included de-spiking, slice timing and motion correction, brain extraction, non-linear spatial normalisation, spatial smoothing (6mm FWHM), band-pass filtering (0.01 to 0.08Hz), linear and quadratic detrending, and regression of nuisance signals. Synchrony between three seed regions (posterior cingulate cortex, anterior insula, and amygdala) and the whole brain were examined. Higher level analyses compared placebo and kisspeptin conditions using FSL's FEAT in a mixed effects cluster corrected ($z>2.3$, $p<0.05$) analysis. No effect was observed in the DMN/Executive network. However, in the salience network (anterior insula seed) kisspeptin decreased synchronous activity between the anterior insula and primary visual areas, compared to placebo. Conversely, for the amygdala seed kisspeptin increased synchrony in the middle cingulate gyrus, compared to placebo. Kisspeptin does not have a global effect on the resting brain, but a focal effect in specific networks. Kisspeptin modulates functional connectivity in key limbic and perception areas even at rest. This suggests kisspeptin acts as an emotional modulator in the human brain.



Contact email address: lysiad@msn.com

Poster number: P-W152
Theme: Neuroendocrine & autonomic systems

Methylprednisolone treatment dysregulates clock gene expression and alters circadian rhythmicity in locomotor activity and body temperature in rat

Authors: Matthew T. Birnie, Benjamin P. Flynn, Amitesh Pratap, Yvonne M. Kershaw, Becky L. Conway-Campbell, Stafford L. Lightman - *School of Clinical Sciences University of Bristol*

Chronic treatment with the synthetic glucocorticoid (GC) prednisolone has been reported in association with many detrimental health effects. In addition to well-documented adverse metabolic effects and deficits to memory, there is also evidence for sleep disturbances in these patients. Cell experiments have shown that synthetic GCs such as methylprednisolone (MPL) cause an alteration in timing of glucocorticoid receptor (GR) activation, inducing a prolonged GR activation profile in contrast to the rapid and transient 'pulsatile' GR activation associated with the natural GC hormones cortisol and corticosterone. However the effect of MPL treatment on GR activation in vivo, particularly in the brain, is less well understood. Here, we have treated 9-10 week old male Lister Hooded rats with 1mg/ml MPL in drinking water (provided ad libitum). We report that this dose supressed endogenous corticosterone secretion but induced significant hippocampal GR activation during the circadian peak as well as the nadir, consistent with prolonged MPL-induced central GR activation. Transcriptional profiling of total RNA from whole hippocampus revealed significant dysregulation in circadian rhythmicity of the clock gene expression network in MPL treated rats, compared to controls. Period1, which is important for the maintenance of circadian rhythm, increased to maximal mRNA expression levels at ZT10-18 in control rats as expected. Notably, MPL treated rats exhibited elevated and phase-shifted mRNA expression throughout. Further dysregulation of the circadian clock was evident in Per2 (ZT10), Cry1 (ZT22-2), Bmal1 (ZT10-14) and Rev-erbα (ZT6-10). At the functional level, we report that locomotor activity and core body temperature were significantly dysregulated with MPL treatment. The characteristic circadian (24hr) rhythm, evident in vehicle treated rats, reverted to a predominant ultradian (4hr) rhythm in MPL treated rats. Our data strongly supports the conclusion that MPL treatment acts centrally to disrupt the molecular circadian clock via a direct GR-dependent mechanism, to cause sleep disturbances in patients treated with prednisolone and other synthetic GCs.

Contact email address: matthew.birnie@bristol.ac.uk

Poster number: P-W153
Theme: Neuroendocrine & autonomic systems

Investigating the function of MR and GR: Defining the scope and function of MRGR interaction using luciferase assays

Authors: Susana Paul, John Pooley, Stafford Lightman - *Henry Wellcome Laboratories for Integrated Neuroscience and Endocrinology (HW LINE), Faculty of Health Sciences University of Bristol*

Glucocorticoids act through two receptor systems namely, the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). Both receptors are co-expressed in the hippocampus and understanding how gene regulation by MR and GR is disrupted when the balance of these activities is changed is vital. Previously, luciferase reporter assays have investigated how MR+GR cooperatively act utilising different cell types, promoter constructs, receptor cDNAs and hormone doses. Findings have been inconsistent regarding the cooperative role of MR+GR relative to either receptor alone.

We performed transient transfections into COS-1 cells (no endogenous receptors) to further investigate cooperative MR+GR function. A firefly luciferase driven by the GRE-containing MMTV LTR sequence provided expression data from Promega's dual-luciferase reporter assay system while western blot determined receptor expression levels in similar transfections.

Transfecting rat MR or GR alone, or co-expressing MR+GR, we found the reported cooperative outcome for MR+GR was dependant on the approach used to adjust the total plasmid DNA to a constant amount. When equivalent picomolar amounts of each plasmid were used, and EGFP substituted for MR or GR in controls, co-expressed MR+GR appeared synergic. A second approach used equivalent nanogram amounts of plasmids with total DNA adjusted to 1 microgram with pcDNA3. This produced an additive response in MR+GR samples where the sum of the individual receptor contributions defined the output.

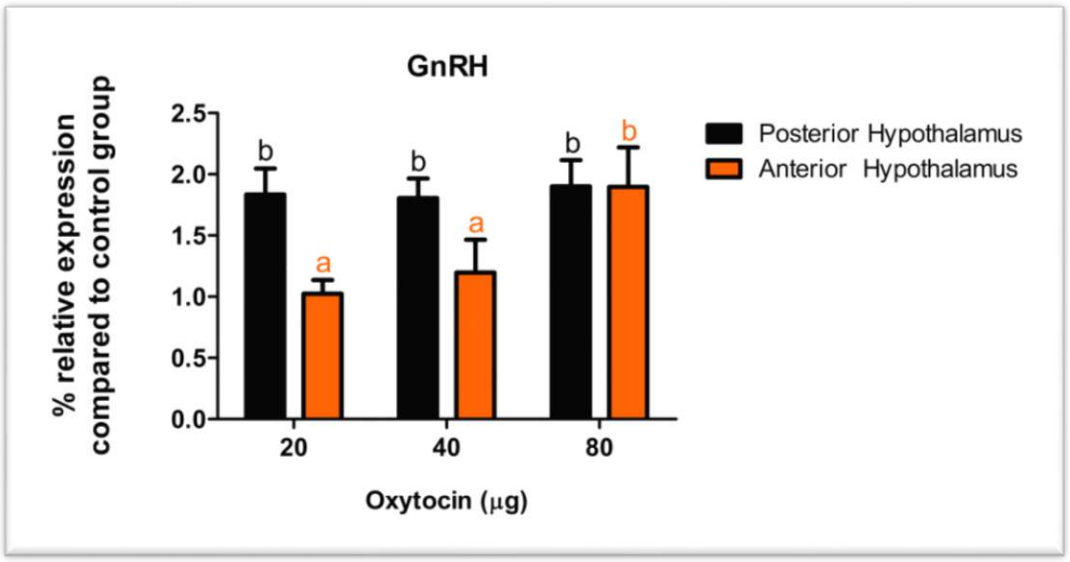
Contact email address: sp16734@bristol.ac.uk

Poster number: P-W154
Theme: Neuroendocrine & autonomic systems

Oxytocin intranasal administration affect neural networks upstream of GnRH neurons

Authors: Mohammad Saied Salehi, Homayoun Khazali - *Animal Physiology Shahid Beheshti University*, Fariba Mahmoudi - *Biology University of Mohaghegh Ardabili*

The last decade has witnessed a surge in research investigating the trial application of intranasal oxytocin as a method of enhancing social interaction in human, although all aspects of its effects are not well understood. Since anxiolytic effects of oxytocin are completely identified in animals that also reported in human, we hypothesized that, at least part of the described effects of oxytocin might be mediated by gonadotropin-releasing hormone (GnRH) as a key reproductive neuroendocrine pathway of social behavior. Accordingly, we evaluated effects of different levels of oxytocin following intranasal administration on GnRH expression in the male rat hypothalamus. In addition, we assessed expression of two excitatory (kisspeptin and neurokinin B) and two inhibitory (dynorphin and RFamide related peptide-3) neuropeptides upstream of GnRH neurons as a possible messengers. Here, twenty four adult male rats received 20, 40 or 80 µg oxytocin intranasally for 10 days and then posterior (PH) and anterior (AH) hypothalamus dissected for evaluation of target genes. In the PH, all three levels of oxytocin, elevated GnRH expression; although in the AH, only the highest dose of the treatment was effective. Also Kiss1 mRNA was decreased in the PH whereas no expression change was detected in the AH. Moreover, basal level of neurokinin B mRNA was increased by intranasally applied oxytocin, however these treatments did not affect the expression of dynorphin mRNA. Only the highest dose of 80 µg oxytocin produced a significant decline in RFRP mRNA expression. Our findings revealed that at least part of oxytocin effects might be mediated by GnRH system.



Contact email address: saied.salehi@gmail.com

Poster number: P-W155
Theme: Methods and techniques

Simulating Electric Field Stimulation with the Virtual Electrode Recording Tool for Extracellular Potentials (VERTEX)

Authors: Chris Thornton, Frances Hutchings, Marcus Kaiser - *School of Computing Science / Institute of Neuroscience Newcastle University*

VERTEX, a MATLAB tool, provides an easy to use environment for the simulation of local field potentials (LFPs) generated by spatially organised spiking neural networks consisting of thousands to hundreds of thousands of neurons [1]. In its second release it will provide support for easily incorporating the effects of electric field stimulation and including synaptic plasticity (short term plasticity as well as spike time dependent plasticity). Here we present details of our implementation and two use cases for our software.

As VERTEX simulates neuronal networks positioned in three dimensions we calculate the electric field across the geometry of our model using the finite element method provided by MATLAB's partial differential equation toolbox. The "Mirror Estimate" is used as an approximation of the membrane polarisation caused by the extracellular electric field. This has been shown to provide an accurate estimate of the effect of point stimulation and of a uniform electric field [2].

To demonstrate the use of our tool we will use a rat neocortical slice model based on experimentally derived anatomy and physiology taken from the the Neocortical Microcircuit Collaboration Portal. We will investigate the LFP response to paired pulse stimulation at a range of frequencies and compare this to equivalent experimental data. We will also present an example of the application of a direct current uniform field and an alternating current field to our neocortical slice model.

[1] Tomsett, R. J., et al (2015). Virtual Electrode Recording Tool for EXtracellular potentials (VERTEX): comparing multi-electrode recordings from simulated and biological mammalian cortical tissue. Brain Struct Funct, 220(4), 2333–2353.
[2] Joucla, S., & Yvert, B. (2009). The "mirror" estimate: An intuitive predictor of membrane polarization during extracellular stimulation. Biophysical Journal, 96(9), 3495–3508.

Contact email address: c.thornton@newcastle.ac.uk

Poster number: P-W156
Theme: Methods and techniques

Establishing methods for quantifying synaptic connectivity at both the meso- and micro-scale in the mouse brain.

Authors: Diana Lucaci - *Life Sciences Imperial College London*, Jun Song, Dr Paul Chadderton - *Bioengineering Imperial College London*, Dr Stephen Brickley - *Life Sciences Imperial College London*

We currently lack high-resolution data from animal models that could identify differences in both synaptic number and synaptic strength. Our laboratories are concerned with establishing a strategy for mapping differences in the strength of synaptic connectivity in defined axonal projections in combination with changes in anatomical connectivity. In this study, we have utilised optogenetics to demonstrate clear differences in the strength of synaptic connectivity in the cortiocollicular projections from primary auditory cortex (AC) to contralateral and ipsilateral dorsal cortex of the inferior colliculus (cDCIC & iDCIC). As well as using this optogenetic approach to map the strength of connections, we have also taken advantage of a novel tool to selectively label synapses with GFP, the mammalian GFP reconstitution across synaptic partners (mGRASP). In accordance with the results from optogenetic mapping, we found that the AC projection to the iDCIC made a larger number of synaptic contacts than to the cDCIC. This study demonstrates the feasibility of combining optogenetic mapping and mGRASP to quantify changes in synaptic connectivity at both meso- and micro-scopic scale.

Contact email address: dl1910@imperial.ac.uk

Poster number: P-W157
Theme: Methods and techniques

A Hierarchical mixture model of decision making with different noise processes in a population of subjects

Authors: Elena Zamfir, Peter Dayan - *Gatsby Computational Neuroscience Unit UC*L ,Molly Crockett - *Oxford Centre for Neuroethics University of Oxford*

There is an increasing wealth of intricate model-based analyses of behavioural and neural data in complex decision-making tasks performed by diverse populations of young and old, healthy and patient subjects. Typically, entire experimental datasets are modelled as a whole, under a hierarchical generative model: this specifies population parameters that govern the distribution of parameters for individual subjects, which in turn determine the distribution of the responses for those subjects. Conventional such schemes capture within subject variability very competently, but suffer from an impoverished model of individual differences, shoehorning them into a simple distributional form. This is a significant problem, for instance, for the otherwise attractive suggestion that the statistical structure of the posterior distributions over the parameters can be a meaningful contributor to a new form of psychiatric nosology.

The next more sophistcated model involves a mixture at the level of the population parameters. One common way to treat these makes the severe approximation of fitting each element of the mixture separately to the entire dataset; this over-regularizes the mixture components. We consider the full problem of simultaneously inferring the responsibilities that each mixture component takes for each subject and the parameters of the components, paying particular attention to different noise models in the choice generating processes of different components, and also to models with different degrees of flexibility. The inversion of such hierarchical models is often intractable, and additional difficulties appear due to the different types of noise, therefore approximations and sampling techniques are used.

We illustrate our approach on simulated data, comparing different schemes, and also fit data from a previously-published decision-making task in which the categorical refusal of some, but not other, subjects to perform a particular class of (cruel) actions led to the need for multiple noise models.

Contact email address: elena@gatsby.ucl.ac.uk

Poster number: P-W158
Theme: Methods and techniques

A comparison study of food or water restriction for behavioural testing in mice

Authors: Emma Yhnell - *Neuroscience and Mental Health Research Institute Cardiff University*, Stephen Dunnett, Simon Brooks - *The Brain Repair Group Cardiff University*

Food or water restriction regimes are often used in the operant behavioural testing of rodents, to motivate learning. Food restriction has been shown to improve health, extend lifespan and modify behavioural results in wildtype and genetically modified mice. However, few studies have been conducted regarding the use of water restriction in mice and a limited number of studies have directly compared food or water restriction for behavioural testing in mice to determine which is most beneficial to the welfare of the animal.

14 male C57BL/6 mice (n = 7 in each group) were obtained from Harlan. Animals were food restricted to 90% of their free feeding body weight. Water restriction was introduced gradually and maintained at 3 hours given per day, after behavioural testing. All animals were either food or water restricted for 5 days prior to behavioural testing. Behavioural testing was conducted in 9-hole operant boxes. Animals were trained to respond on a simple fixed ratio schedule of one response for one reward. Initial testing was conducted for 28 days. Animals were given a 4 day rest period, then the restriction was then reversed for 15 days.

The results demonstrated no statistically significant differences in the overall number of nose poke responses observed between food or water restricted animals. However, upon the reversal of the restriction regime, food restricted animals lost significantly more weight in comparison to water restricted animals ($F_{1,21} = 11.75$, $p<0.01$).

In conclusion, our results demonstrate that water restriction produces consistent behavioural results and causes comparatively less weight loss than food restriction, in the operant behavioural testing of mice. These results have important implications for refining restriction regimes, producing consistent and reproducible behavioural results and in providing the least detrimental restriction regime for the welfare of animals.

Acknowledgement: This work was funded by an MRC PhD Studentship awarded to Emma Yhnell

Contact email address: YhnellE@cardiff.ac.uk

Poster number: P-W159
Theme: Methods and techniques

Utilizing analytical biochemistry techniques to interrogate the state of tissue metabolism during mitochondrial epilepsy

Authors: Felix Chan - *Institute of Neuroscience Newcastle University*, Caroline Marie Voss - *Department of Drug Design and Pharmacology University of Copenhagen*, Nichola Lax - *Wellcome Trust Centre for Mitochondrial Research Newcastle University*, Blanca Irene Aldana Garcia - *Department of Drug Design and Pharmacology University of Copenhagen*, Ceri Davies - *Singapore R&D Site (formerly) Glaxo Smith Kline (formerly)*, Doug Turnbull - *Wellcome Trust Centre for Mitochondrial Research Newcastle University*, Helle S Waagepetersen - *Department of Drug Design and Pharmacology University of Copenhagen*, Mark O Cunningham - *Institute of Neuroscience Newcastle University*

We have developed a novel in vitro brain slice model for mitochondrial epilepsy based on neuronal respiratory chain inhibition using rotenone (complex I inhibitor) and cyanide (complex IV inhibitor) as well as astrocytic Krebs cycle inhibition using fluorocitrate (astrocyte-specific aconitase inhibitor). We aim to characterize the metabolic state of the tissue during the seizure state by labelling with [U-13C]-glucose. Quantification of the amount of relevant amino acids is performed using HPLC and tracing of the metabolic labelling of the 13C using GC-MS. There is significant increase in alanine and lactate pool in the epileptic slices, suggesting significant upregulation of glycolytic activity. 13C labelling indicates that in addition to upregulation of glycolysis, there is also significant increase in the pentose-phosphate-pathway suggesting the generation of NADPH, an important cellular reducing-agent against oxidative stress. Krebs cycle activity is significantly reduced, as demonstrated by reduced labelling in α-ketoglutarate, fumarate, malate, and succinate. Accumulation of labelled citrate confirmed a severe block in aconitase. Glutamate and GABA pool is increased, suggesting the lack of use of these metabolic substrates for energy production. Interestingly, glutamine pool is significantly depleted in epileptic slices, showing a preferential use of glutamine as metabolic fuel during a seizure state. Pool size of branched chain amino acids (leucine, valine, and isoleucine) is also increased, again suggesting the inability to utilize these amino

acids as energy source. Our results indicate severe metabolic changes that occur during the seizure state in mitochondrial epilepsy. In particular, several pathways are implicated such as the astrocytic glutamate-glutamine cycle and anaerobic glycolysis. Analytical biochemistry techniques represent a novel approach towards interrogating changes in tissue metabolism during a seizure state.

Contact email address: f.chan2@ncl.ac.uk

Poster number: P-W160
Theme: Methods and techniques

Efficient isolation of viable primary neural cells from adult murine brain tissue based on a novel automated tissue dissociation protocol

Authors: Hui Zhang - *R&D Miltenyi Biotec GmbH*

Tissue dissociation and preparation of single-cell suspensions with high cell viability and a minimum of cell debris are prerequisites for reliable cellular analysis, cell culture, and cell separation. As dissociation of adult brain requires sophisticated mechanical and enzymatic treatment to successfully disaggregate the tightly connected neural cells, cell analysis is often restricted to embryonic or neonatal rodent tissue. We have set up technologies for dissociation of neonatal brain by combining automated mechanical dissociation using the gentleMACS™ Octo Dissociator with an optimized enzymatic treatment. To extend the analyses to adult neural cells we have further optimized the method by including a novel protocol for removal of debris and erythrocytes, which is crucial for effective cell isolation and culture.

The standardized process allows fast and reproducible dissociation of adult murine brain tissue and was optimized to increase the number of viable cells. Protocols for the magnetic isolation (MACS® Technology) of astrocytes, oligodendrocytes, neurons, microglia, and endothelial cells to high purities were also established and cultivation conditions were optimized to sucessfully cultivate adult neural cell populations. Furthermore, highly purified astrocytes were subjected to single-cell mRNA sequencing analysis in order to characterize neonatal and adult astrocyte diversity. In summary, we present a novel standardized technology to generate highly purified and viable adult neural cells that extends the analysis from neonatal to adult murine brain tissue and facilitates sophisticated cellular and molecular analyses.

Contact email address: huiz@miltenyibiotec.de

Poster number: P-W161
Theme: Methods and techniques

Simulation of sleep in a mouse: regional and light-dark differences in the dynamics of sleep homeostasis

Authors: Mathilde Guillaumin - *Nuffield Department of Clinical Neurosciences University of Oxford*, Laura McKillop, Nanyi Cui, Simon Fisher - *Department of Physiology, Anatomy and Genetics University of Oxford*, Stuart Peirson - *Nuffield Department of Clinical Neurosciences University of Oxford*, Peter Achermann - *Institute of Pharmacology and Toxicology University of Zurich*, Vladyslav Vyazovskiy - *Department of Physiology, Anatomy and Genetics University of Oxford*

The two-process model of sleep describes the interaction between a sleep/wake dependent ‘Process S’ and a circadian ‘Process C’ regulating the timing, duration and intensity of sleep episodes. Traditionally, the dynamics of Process S are inferred from the distribution of sleep and waking over 24h periods, and empirical values of electroencephalogram (EEG) slow-wave activity (SWA, 0.5-4 Hz) are used to estimate the time constants of Process S. The aims of the present study were to adapt an elaborated version of the two-process model to mouse EEG recordings and to investigate the influence of the brain region and the time of day on the dynamics of Process S.

To that end, the vigilance states from undisturbed 48-h EEG recordings performed in 9 adult male C57BL/6J mice were annotated. EEG electrodes were implanted in the occipital and frontal regions of the neocortex. All analyses were based on 4-s epochs.

The time course of SWA was successfully simulated on a time-scale of 24 h, but also, for the first time in mice, within individual episodes of non-rapid eye movement sleep. The applicability of the two-process model to EEG recordings obtained in mice was confirmed by the close fit obtained between empirical and simulated SWA levels. The discrepancy between simulated and empirical data was consistently smaller during the light phase than in the dark phase, in both occipital and frontal derivations (Frontal derivation: Light=7.7±1.4%, Dark=17.4±1.4%, $p<0.001$; Occipital derivation: Light=7.6±1.0%, Dark=12.7±1.3%, $p<0.01$, mean±SEM).

The decay rate of Process S was significantly different between derivations, attaining higher values in the frontal region (Frontal: 10±1x10-4 epoch-1, Occipital: 7±1x10-4 epoch-1, p<0.01, mean±SEM).

Overall, the results suggest regional inhomogeneity in the dissipation of sleep pressure across the brain, which supports the notion of local sleep regulation. Furthermore, the light/dark differences in the goodness of fit may reflect the impact of specific waking behaviours, lighting conditions or a direct influence of the circadian clock on the build-up or dissipation of sleep-pressure.
Acknowledgements: BBSRC, MRC, Wellcome Trust, Clarendon, SNSF.

Contact email address: mathilde.guillaumin@chch.ox.ac.uk

Poster number: P-W162
Theme: Methods and techniques

Delivery of Nucleic Acids for Modulating Neuronal Gene Expression in vitro and in vivo Using Lipid Nanoparticles

Authors: Richard Broadhead - *Research and Development Precision Nanosystems*

Demand for an efficient delivery tool capable of delivering payloads for modulating gene expression in vitro and in vivo has been growing. Of the tools available, developments in the field of lipid nanoparticles (LNPs) have allowed for the reliable and efficient delivery of nucleic acids, both in research and clinical settings. Here, we bridge that gap by describing the development of an LNP delivery system for nucleic acids, robustly manufactured with clinical-grade materials using microfluidic technology at scales for screening applications, in vitro experiments and research in animals. We describe the use of lipid-based nanoparticles for highly efficient encapsulation and delivery of payloads, such as siRNA, mRNA and plasmid. In this proof of concept, we show that representative small RNAs, mRNAs and plasmids can be successfully delivered to primary neurons. LNPs manufactured to encapsulate various nucleic acids can do so with high efficiency, encapulating more than 95% of the payload, minimizing payload loss. Transfection efficiency of the LNPs is >95%, quantified using a flourescent dye. The biological endpoint assays used to determine the accessiblility of the payloads delivered varies for siRNA, mRNA and plasmid. Using doses of 1 g per mL of media, we achieved >90% knockdown with siRNA delivery, >90% of the primary neurons are GFP+ with GFP mRNA delivery and >60% of the primary neurons are GFP+ with GFP plasmid delivery. The LNPs are well tolerated, such that 5x the required doses have no oberservable cytoxicity. We show that the LNPs can also be used to deliver payloads into various regions of the animal brain. The localized injections into the cortex and the striatum are well tolerated and have extensive distribution. These validation studies provide suitable insights in establishing strategies for efficiently delivering nucleic acid payloads into primary cultures and into the animal. The use of LNPs can be extrapolated to other applications such as delivery of CRISPR-Cas9 components with a simple change in payload.

Contact email address: rbroadhead@precision-nano.com

Poster number: P-W163
Theme: Methods and techniques

Standalone Headstage for Neural Recording with Real-Time Spike Sorting and Data Logging

Authors: Song Luan, Ian Williams - *Electrical and Electronic Engineering Imperial College London*, Felipe De-Carvalho - *Institute of Neuroscience Newcastle University*, Laszlo Grand - *Electrical and Electronic Engineering Imperial College London*, Andrew Jackson - *Institute of Neuroscience Newcastle University*, Rodrigo Quian Quiroga - *Centre for Systems Neuroscience University of Leicester*, Timothy Constandinou - *Electrical and Electronic Engineering Imperial College London*

Recording neurophysiological correlates of behaviour is essential for understanding modus operandi of behaviour specific neuronal circuits and functional connectivity between various brain areas. Achieving this goal requires significant technological advancement, as 24/7 recording of action potentials from large number of neurons in freely moving animals during the natural sleep-wake cycle is highly demanding. Chronically implantable high-density neural interfaces provide action potentials from many neurons, however as channel counts increase, the data bandwidth and power dissipation of implantable electronics present a major bottleneck. This work develops a miniature neural logging system with on-node spike sorting achieving a massive data reduction.

We have developed a 2-stage approach in which first; raw data is collected and spike templates identified off-line using established spike sorting software (WaveClus). Spike parameters are then uploaded to custom template matching hardware implemented in

low power FPGA platform. The algorithm has been designed to provide an optimal balance between power consumption (i.e. complexity) and performance. The digitised raw data, detected action potentials snippets, and/or timestamped sorted events can then be streamed onto a high capacity microSD card. The headstage also provides a real-time (0.3ms latency) spike event output to a digital bus (SPI) for closed-loop applications, e.g, to trigger electrical or optogenetic stimulation.

The current hardware provides 32-channels of amplification, filtering, and real-time spike detection and sorting (4 templates/ch) with a total power of under 40mW. Data (raw data/spikes/events) can be streamed via USB to a PC running a custom GUI for display, or stored onto a microSD card logger. We have successfully tested the system to obtain 24-hour real-time spike recordings from monkey cortex.

Conclusions. The system will in future support wireless configuration and monitoring instead of USB connection. This will allow the user to setup the system and actively monitor the data without impeding on a freely-behaving animal. We anticipate this will provide a key component enabling future high-channel wireless recording systems and closed-loop neuroprostheses.

EPSRC-funded.

Contact email address: s.luan@ic.ac.uk

Poster number: P-W164
Theme: Methods and techniques

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

Authors: Steven Jerjian, Stephan Waldert, Roger Lemon, Alexander Kraskov - *Sobell Department of Motor Neuroscience & Movement Disorders UCL Institute of Neurology*

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

Numerical simulations were based on a previous study in which 100 datasets of “noise” (1/(f^α) pink noise, α=1.4) and “noise+spikes” (same noise plus spike waveforms extracted from recorded neuronal data) were created(1). FFT amplitudes across pairs of “noise” vs. “noise+spikes” were compared before and after spike removal, with p-values used to fit a risk zone curve for spike contamination in an LFP frequency vs. spike rate plane. The real dataset was comprised of recordings in cortical motor areas of two rhesus macaques during a reach-to-grasp movement task(4).

Spiking activity was always identified by high-pass filtering and thresholding(5). A sliding median filter (width 3ms) was applied to 1.5ms windows around detected spikes.

Spectral power <300Hz attributable to spike contamination was significantly dampened following median filtering. This shifted the risk zone for spike contamination towards higher LFP frequencies, and improved coherence estimates between artificial signals. In the real dataset, median filtering reduced gamma power (60-100Hz) caused by spiking activity.

This study demonstrates the potential use of median filtering as a better alternative to linear filters for separating spikes and LFP. This simple method easily removes spikes from the signal with minimal artefact introduction and does not require spike sorting. Further studies may investigate more advanced median filters to improve retention of desired signal components.

References

1. Waldert et al. J Physiol 591, 5291-303 (2013).
2. David et al. Comput. Intell. Neurosci. 2010, (2010).
3. Zanos et al. J Neurophysiol. 105, 474-86 (2011).
4. Waldert et al. J Neurosci. 35, 8451-61 (2015).
5. Quiroga et al. Neural Comput. 16, 1661-87 (2004).

Contact email address: steven.jerjian.11@ucl.ac.uk

Poster number: P-W165
Theme: Methods and techniques

Modelling GCaMP responses: From spikes to fluorescence

Authors: Thomas Delaney - *School of Computer Science University of Bristol*, Dr. Mike Ashby - *School of Physiology and Pharmacology University of Bristol*, Dr. Cian O'Donnell - *School of Computer Science University of Bristol*

The use of fluorescent calcium indicators, such as GCaMP6 to monitor neuronal activity is widespread. But relationship between GCaMP6 fluorescence and action potential firing is poorly understood. Furthermore, the effects of the indicator characteristics on this fluorescence signal are unknown. For example, it is known that the GCaMP indicator accumulates within neurons over weeks and months, which creates difficulties in comparing activity statistics across timepoints. As a result, whether or not spike train inference is always possible using GCaMP6 fluorescence remains unknown.

The aim of this project was to simulate the fluorescence traces produced by a fluorescent calcium indicator in a neuron soma, given parameters such as binding rate, dissociation rate, and molecular concentration from a specified spike train. The ultimate goal of the simulations were to allow benchmarking of the various spike inference algorithms that thave been developed (Theis et al, 2016), and to understand how indicator characteristics affect the quality of spike train inference.

The modelled cell contents consisted of free calcium, fluorescent indicator molecules, and mobile and immobile endogenous calcium buffers. The indicator molecules which were bound to a calcium molecule could be either excited, i.e. able to release a photon, or relaxed. In order to reproduce the noise in the system dynamics and the photon capturing process, the system was modelled as a piecewise-deterministic Markov process.

The fluorescence traces produced by the simulation were calibrated to reproduce the signal-to-noise ratio of observed in GCaMP6 data (Chen et al, 2013). The noise level was then varied to examine how this affect spike train inference. Then, the parameters of the model, i.e. GCaMP concentration, binding and dissociation rates, and endogenous buffer properties were varied, again to examine the effects on spike inference.

Contact email address: td16954@bristol.ac.uk

Poster number: P-W166
Theme: Methods and techniques

Implantable RF-coil with multiple electrodes for long-term EEG-fMRI monitoring in rodents

Authors: Tiina Pirttimäki, Raimo Salo - *Neurobiology University of Eastern Finland*, Artem Shatillo - *MRI Charles River Discovery Services,* Mikko Kettunen, Jaakko Paasonen, Alejandra Sierra, Kimmo Jokivarsi - *Neurobiology University of Eastern Finland*, Ville Leinonen - *Neurosurgery Kuopio University Hospital*, Pedro Andrade - *Neurobiology University of Eastern Finland*, Simon Quittek - *Engineering RAPID Biomedical GmbH*

Background
Simultaneous EEG-fMRI is a valuable tool in the clinic as it provides excellent temporal and spatial information about normal and diseased brain function. In pre-clinical research with small rodents, obtaining simultaneous EEG-fMRI in longitudinal studies faces a number of challenges, including issues related to magnetic susceptibility artifacts. The aim of this study was to develop a method that would allow us to conduct long-term follow-up studies using video-EEG and EEG-fMRI in order to investigate dynamic cortical and subcortical network changes during brain injury.

Methods
We used screw-free method for the chronic implantation of radiofrequency coil (RF-coil) and EEG electrodes in adult Wistar rats. First, the RF-coil/EEG electrode set-up was tested for several months for the coil (7T) and EEG function. Then, to examine changes before and after a brain injury, a group of rats were subjected to chemically induced epileptogenesis using systemic injection of kainic acid.

Results
Our findings showed that the screw-free implantation method is well suited for long-term follow-up studies in both freely moving video-EEG settings and fMRI without causing MRI susceptibility artifacts. Furthermore, the results demonstrated that a multimodal approach can be used to track the progression of structural and functional changes.

Conclusion
This new multimodal EEG-fMRI approach provides a novel tool for concomitant analysis and follow-up of anatomic and functional MRI, as well as electrographic changes in a preclinical research

Contact email address: tiina.pirttimaki@uef.fi

Poster number: P-W167
Theme: Other (e.g. teaching, history, outreach)

Kymata Atlas Dataset 3.01: Raw, publicly available, EMEG data

Authors: Andrew Thwaites - *Department of Psychology University of Cambridge*, Ian Nimmo-Smith - *MRC Cognition and Brain Sciences Unit*, Eric Wieser - *Department of Engineering University of Cambridge*, Andrew Soltan - *School of Clinical Medicine University of Cambridge*, William D. Marslen-Wilson - *Department of Psychology University of Cambridge*

Background
The Kymata Atlas is a database of information processing in the human brain (Thwaites *et al.*, 2015). The information in this database is generated from electro-magnetoencephalographic recordings, taken from healthy subjects. The participants are asked to watch a sequence of moving dots and listen to a podcast (without any further tasks asked of them) during this period. These raw recordings – and the estimates of dendritic current that gave rise to them – are being made available so that other researchers can use them in their own research.

Methods
15 right-handed participants were recruited. All gave informed consent and were paid for their participation. The study was approved by the Peterborough and Fenland Ethical Committee (UK). Audio and visual stimuli (both lasting 6 minute 40 second) were presented simultaneously. The auditory stimulus was a BBC Russia radio interview about Colombian coffee (presented at a sampling rate of 44.1 kHz with 16-bit conversion.) The visual stimulus was a pattern of randomly placed dots with a grey mask in the surrounds and centre. The colour and horizontal movement of these dots fluctuated pseudo-randomly. 10 seconds of stimulus were added to the beginning and end of the stimulus to avoid edge effects. The continuous 6 minute 40 second stimulus was presented four times. The continuous MEG data were recorded using a 306 channel VectorView system. Simultaneous EEG data was recorded from 70 Ag-AgCl electrodes. The locations of the cortical current sources were estimated using Minimum-Norm estimation. Source activations for each trial were averaged over participants.

Results and conclusion
The Kymata measurement datasets are made available under a Creative Commons Attribution 4.0 International License. They are available for download at https://kymata.org/datasets.

References
Thwaites, A., Nimmo-Smith, I., Wieser, E., Soltan, A., & Marslen-Wilson, W. D. (2016) *Measurement datasets 1-3.01 for the "Kymata Atlas"* [dataset]. doi: 10.17863/CAM.1660
Thwaites A, Wieser E, Soltan, A., Nimmo-Smith, I. and Marslen-Wilson, W. D. (2015) "The Kymata Atlas: visualising the information processing pathways of the human brain", [Abstract] *BIH*, London.

Contact email address: acgt2@cam.ac.uk

Poster number: P-W168
Theme: Other (e.g. teaching, history, outreach)

An investigation into the relationship between intelligence beliefs, study stress and smart drugs in UK undergraduate students

Authors: Eleanor J. Dommett, Benjamin D. Gardner - *Psychology King's College London*, Jacqueline Champagne - *Psychosis Studies King's College London*

Smart drugs are prescription drugs taken by individuals, either without a prescription or at a higher dose than prescribed, intending to improve their cognitive abilities, usually in the context of academic achievement. Empirical research has examined the prevalence of smart drug use among student populations, with consistent reports of around 16% using the drugs at some point.

However, what exactly is driving these individuals to engage in the activity has been relatively unexplored and remains unclear. This anonymous online investigation used a modified Perceived Stress Scale and Theory of Intelligence Scales to examine whether students experiencing certain levels of stress and holding specific intelligence beliefs were more likely to be aware of, hold more positive attitudes towards and use, smart drugs. To date, over 150 UK full-time undergraduates have participated.

In line with previous research, 14% of participants reported having taken smart drugs, of which the majority reported using modafinil. The most common reason given for use was 'to look smart'. An independent-samples t-test revealed that, compared to non-users, users were significantly more aware of other students using smart drugs and using them at intense study times, spoke more with students about them, thought they were less harmful, had a more positive attitude towards using them, and were more likely to use them in the next 12 months. There was a positive correlation between experienced study stress and awareness of others taking smart drugs at intense study periods but no direct relationship between stress and personal use. In terms of intelligence beliefs, although no relationship was found with use, students holding a fixed, as opposed to an incremental view of intelligence, were more likely to have spoken to other students about their use.

In summary, the results so far indicate that students using smart drugs generally have a higher awareness of their use by others, communicate more about the drugs and perceive them as safer than students not using them. There appear to be no direct relationships between stress and intelligence beliefs and smart drug measures, but it is possible that peer interactions may impact on this.

Contact email address: eleanor.dommett@kcl.ac.uk

Poster number: P-W169
Theme: Other (e.g. teaching, history, outreach)

The Brain Domain – Science Writing for Public Engagement

Authors: Kira Rienecker - *Psychological Medicine & Clinical Neuroscience Cardiff University*

The information age has propelled scientific progression into the public eye, and the pursuit of advancing knowledge is no longer a closed topic. The academic world has been relatively slow to adapt, but recently we have begun to see institution focused interest in public engagement. As this change occurs, it is becoming apparent that effective science communication is gradually becoming another criteria of the modern scientist. Several grant funders and institutes now require researchers to engage in science communication, and actively seek this skill during recruitment. Yet for those of us at the beginning of our careers, communicating high level concepts to a lay audience in a non-academic way is an untrained skill. Furthermore, existing outlets for science communication to build these skills tend to be inflexible and highly time consuming.

The Brain Domain is a blog and article focused public engagement website, geared towards helping young neuroscientists improve their skills in science writing and communication. It is designed to take advantage of an active writing community to collectively edit and improve our science writing skills. We aim to achieve this in a way which does not interfere with work, and subsequently have no required publishing quotas, which means writers can submit articles when they have spare time or inspiration. Additionally, this enables the writer to determine how involved they want to be. Whilst there are general guidelines and article structures, we want to encourage writers to explore any topic of neuroscience they are interested in. This is enabled through communal editing, to improve both readability and scientific accuracy. The Brain Domain also benefits from an in-house lay editor, who can offer advice on structure and lay understanding. The Brain Domain is free, however we rely on social media to improve our impact and reach, and ask that writers occasionally promote articles other than their own.

Organisation & Website: www.thebraindomain.org

Contact email address: rieneckerkd@cardiff.ac.uk

Poster number: P-W170
Theme: Other (e.g. teaching, history, outreach)

N400 potential as marker of human beliefs

Authors: Patrycja Delong - *Psychology University of Birmingham*

Questionnaire based assessment of one's beliefs is a subjective measure and as such is prone to errors. This is especially true for religious beliefs because of their personal character and importance, which can affect subject's capability of accurate self-evaluation and influence willingness to reveal own honest opinions [1].
In this study event-related potentials were considered as an alternative approach to religiosity measurement. N400 potential classically is interpreted as linguistic component, that appears in response to semantic incongruency [2], however it also has been shown to emerge in response to statements, which violated common knowledge [3].
During EEG registration participants were presented with religious and atheistic statements created based on popular religiosity questionnaires. Additionally, they completed two standard questionnaires: Individual Religiosity Scale and Supernatural Belief Scale, which were used to assign subjects to one of three groups: religious, atheistic and neutral.
In response to religious statements we observed significantly greater N400 amplitude in atheistic than religious group, but amplitude of the potential in response to atheistic statements did not differ between groups. For intergroup comparisons N400 amplitude was greater for atheistic than religious statements within religious group, but no difference was observed within atheistic group.

In atheistic group strong N400 emerged in response to both religious and atheistic statements, which suggests that they also disagreed with our atheistic statements. This is probably due to the character of atheistic statements used, which were constructed by analogy to religious ones i.e. "It is important to me for my children to be raised as Christians/atheists", which is not necessarily as relevant for non-believers as for believers.

1. Hill, P. C. & Maltby, L. E. in 33–50 (2009).
2. Lau, E. F., Phillips, C. & Poeppel, D. A cortical network for semantics: (de)constructing the N400. Nat. Rev. Neurosci. 9, 920–933 (2008).
3. Lindeman, M. et al. Sentences with core knowledge violations increase the size of N400 among paranormal believers. Cortex 44, 1307–1315 (2008).

Contact email address: patrycja.delong@gmail.com

Poster number: P-W171
Theme: Other (e.g. teaching, history, outreach)

A Brain Museum Tour of Europe

Authors: Richard Brown - *Psychology and Neuroscience Dalhousie University*

Europe has a rich history of neuroscience research and clinical neurology, but where can the history of European neuroscience be found? The historical artifacts, documents and discoveries of European neuroscience exist in many museums, but these are often forgotten or neglected within Europe and relatively unknown outside of Europe. The purpose of this project is to present a tour of the brain museums of Europe on a WEBSITE, showing the museums with materials relevant to the history of neuroscience in each country. The history of neuroscience relies of objects from the past and this website describes the collections related to brain research in European museums. Using this website will enable students and researchers to locate historical objects in museums and plan visits to these museums for teaching and research. The presentation will consist of a poster/oral presentation and a website which meeting participants can browse for information. The present poster/Website contains information on 31 brain museums in 18 countries, with more being added as we find them. The website is a work in progress and we hope that users will provide us with information about brain museums which we have not yet discovered. If you are planning a trip to one of the European cities with a brain museum, this website will guide you to the location and the exhibitions on view. Enjoy your tour of Brain Museums in Europe! This project is sponsored by the FENS History of Neuroscience Committee. If you know of brain museums not presented on this poster, please contact Richard Brown at rebrown@dal.ca.

Contact email address: rebrown@dal.ca

Poster number: P-W172
Theme: Other (e.g. teaching, history, outreach)

Today's neuroscience; tomorrow's history: the importance of oral testimonies

Authors: Tilli Tansey, Apostolos Zarros - *History of Modern Biomedicine Research Group, School of History QMUL*

In 2006, a Wellcome Trust grant to L.L. Iversen and E. M. Tansey supported a project to record video interviews (conducted by R. Thomas) with 12 eminent neuroscientists in the fields of neuropharmacology, neuroimaging and neuropsychology [1]. More recently a Strategic Award from the same source has allowed for a further series of audio and video interviews to be conducted with neuroscientists [2], in addition to extending the already well known Witness Seminar series [3]. Our Group studies the history of recent biomedicine principally by employing oral history methodology (with ethical committee approval QMREC 0642) as we generate resources such as individual interviews, Witness Seminars, and other publications and outputs, by collecting, transcribing, editing and publishing oral testimonies from groups and individuals who have made significant contributions to the legacy of modern biomedicine. Neuroscience is a fundamental component of our work, and a significant part of our output is related to neuroscientific research and achievements, with a particular emphasis to meetings and interviews on the development of drugs affecting 5HT systems, the creation of novel treatments for disorders such as migraine, depression, or even seasonal affective disorder, as well as the establishment of brain banks in the UK. This evidence is accompanied by testimonies that shed light on the ways the scientific community has reacted to challenges; the nature and the complexity with which scientific collegiality has been shaped throughout the years; the bureaucratic and legal pitfalls; as well as the role of research funding and industrial relations. We herein present materials gathered through oral history methodologies which provide unique resources that help inform our understanding, contextualization, reconstruction and communication of important aspects of neuroscience as a discipline, and emphasise their significance in the framework of modern biomedicine.

[1]. http://www.histmodbiomed.org/article/todays-neuroscience-tomorrows-history
[2]. http://www.histmodbiomed.org/article/nervous-system-and-neuroscientists
[3]. http://www.histmodbiomed.org/article/wellcome-witnesses-volumes

We thank the Wellcome Trust for support.

Contact email address: t.tansey@qmul.ac.uk

Poster number: P-W173
Theme: Other (e.g. teaching, history, outreach)

A classification system for funding allocations across areas of mental health research

Authors: Virginia Fairclough - *Research Team MQ: Transforming Mental Health*, Cynthia Joyce - *CEO MQ: Transforming Mental Health*, Sophie Dix, Eva Wölbert - *Research Team MQ: Transforming Mental Health*

It is widely accepted that more funding needs to be invested into scientific research for mental health (MH). However, when determining which areas of mental health research are most in need of funding and research development, we must assess the funding allocations across all areas of MH research, whilst identifying areas of greatest need for patients.
MQ: Transforming mental health (MQ) previously mapped out the funding landscape across all facets of MH funding in great detail across all disciplines of MH research, with a publication of findings in 20151. However, the methods involved manual classification of grant records, which is an arduous and highly variable process, thereby highlighting the need for automation and a universally accepted classification system for MH grants. Until now, there were no standard classification criteria for grants within the field of mental health, and classification was not reproducible across funding bodies. Therefore, MQ is developing a new method using the Uber Dimensions database as a tool for devising a standardised method for gathering data and grant categorisation, thereby generating reproducible results. This is crucial for the comparison of grant sets as we track the status of MH research both retrospectively and in the future.

We present this method for grant classification here, alongside the corresponding funding conclusions drawn from the resulting analyses, showing, for example, that the number of UK grants within the areas of depression, anxiety, and substance abuse and addiction were 42, 13 and 18 respectively between April 2014 – March 2016. We subsequently make a case for the need for this standardised classification system in order to coherently determine a funding strategy for long term improvements in MH research via educated investment strategies. It is only with these informed investments in MH research that we can begin to see improvements in clinical outcomes for patients.

1Kirtley, A. MQ: Transforming Mental Health Through Research. (April 2015). Mental Health Research Funding: MQ Landscape Analysis. http://b.3cdn.net/joinmq/1f731755e4183d5337_apm6b0gll.pdf

Contact email address: vfairclough@mqmentalhealth.org