Poster number: P-M001
Theme: Attention, motivation, behaviour

MDMA increases recruitment of social brain areas when interacting with cooperative players during an iterated Prisoner's Dilemma

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Introduction: The iterated Prisoner's Dilemma is used to investigate trust, cooperation and responses to violations of these concepts; one among a number of social decision-making tasks which are increasingly being used to study social cognition. The psychopharmacology of the processes underlying behaviour in these tasks is poorly understood. To address this, we carried out a functional neuroimaging study investigating the effect of the potent serotonergic compound, 3,4-methylenedioxymethamphetamine (MDMA), on cooperation and trust in an iterated Prisoner's Dilemma (iPD).

Methods: Twenty, healthy, male participants were enrolled in to this double-blind, placebo-controlled study. 100mg MDMA or placebo was administered prior to playing an iPD during fMRI scanning. Participants played repeated rounds with 'trustworthy' (mostly cooperative) and 'untrustworthy' (mostly uncooperative) opponents, as well as a non-social control. On each round participants were asked to Compete or Cooperate, received feedback as to the other player's decision, and were asked to rate their trust in the other player.

Results: MDMA increased cooperation when playing the trustworthy opponents (OR = 2.01 (1.46 – 2.96), $p < 0.001$), but not when playing untrustworthy opponents (OR = 1.25 (0.73 – 2.13)) or the non-social control (OR = 1.05 (0.72 – 1.54)). There was no effect of MDMA on trust ratings. When receiving feedback of the trustworthy players' decisions, MDMA increased activity in regions involved with social cognition, including the mid-cingulate gyrus, supplementary motor area, superior temporal sulcus, and bilateral insula. Restricting the analysis to just cooperative feedback from trustworthy players did not appreciably alter the results but revealed increased bilateral putamen activation. No other contrasts showed statistically significant results.

Discussion: Increased engagement of social brain regions on MDMA underlies greater tolerance for untrustworthy behaviour of cooperative partners. Furthermore, higher activation of the putamen in response to cooperative behaviour suggests greater social reward processing on MDMA. These results provide evidence for some opponent and process dependent specificity in the role of serotonin in social interactions.

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Poster number: P-M002
Theme: Attention, motivation, behaviour

The cingulum bundle: backbone of the social brain?

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The cingulum bundle (CB) is a major white matter tract that supports communication between cortical regions within the so-called default-mode network (DMN). While the DMN is classically considered a "task negative network", it has been increasing recognized that there is considerable overlap between components of the DMN and regions involved in social cognition, particularly mental state understanding. While microstructure of the CB has been shown to be related to the functional connectivity of the DMN network, no work has investigated whether these microstructural properties are related to individual differences in mental state understanding. We addressed this gap by investigating the relationship between microstructural properties of the CB and performance on a novel measure of mental state understanding, the Short Story Task (SST). Whole brain high angular resolution diffusion image (HARDI) and SST data were collected for 47 healthy participants. Constrained spherical deconvolution tractography was used to virtually dissect the CB and quantify, via tissue fractional anisotropy (FA), individual differences in the microstructure of

the subgenual and retrosplenial segments of the CB in each hemisphere. We found that FA of the left sub-genual CB was significantly correlated with individual differences in mental state undertanding but not with a control measure of story comprehension, Mental state understanding was not correlated with FA in the retrosplenial CB of either hemisphere. These findings support the proposal that the sub-genual cingulum may support the functional integration of activity between anterior midline cortical regions implicated in mental state understanding and highlight the importance of white matter microstructure to inter-individual variability in social-emotional processing.

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Poster number: P-M003
Theme: Attention, motivation, behaviour

The Neural Correlates of Visual Imagery

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AIM: Visual imagery is a form of sensory imagination characterised by perception-like experiences in the absence of corresponding stimuli. Here, we report a co-ordinate-based meta-analysis of fMRI data that identifies the neural correlates of visual imagery. We will also share some initial results from the application of this method to the analysis motor imagery, and the protocol for a forthcoming study which will explore the neural basis of aphantasia: the absence of visual imagery.

METHOD: Search terms were optimised using the Web of Knowledge and TAPoRware; calculations were performed using the Activation Likelihood Estimation algorithm (ALE, Turkeltaub 2012, implemented in GingerALE, v2.3.5), with a cluster-forming threshold of P=<0.001, and a cluster-level inference threshold of P=0.05 and 1000 repetitions.

RESULTS: Searches identified 1554 papers on the 16th June 2015; on the basis of predetermined inclusion criteria, we extracted data from 45 papers, encompassing 762 foci and 510 participants. An overall comparison based on these studies identified 13 clusters of activation characteristic of visual imagery, within which there were 24 discrete foci. The largest clusters spanned contiguous areas of the left parietal lobule (encompassing BA7, BA40; 11,040mm3) and bilateral frontal areas (BA6; 6,552mm3). Other activations in prominently visual areas included the bilateral lingual gyrus (BA18), the right cuneus (BA17) and precuneus (BA7), and the bilateral fusiform gyrus (BA37). Finally, we found activation in the left claustrum, and both insulae. Differing patterns of activation were observed if the task required a decision based on the image, or accessed different memory systems.

CONCLUSION: Visual imagery activates many of the same areas as visual perception, supporting a depictive interpretation for many of the underlying mental representations. Activity in other areas highlights the diversity of processes involved in the interpretation of these mental representations.

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Poster number: P-M004
Theme: Attention, motivation, behaviour

Social cognition post brain injury: impact of theory of mind impairment on socialization outcome

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Theory of mind ToM is the phenomenon of imputing mental state, emotion, and intention to self and other, and hence, it intensely impacts social interaction competency. Though previous empirical data signify the occurrence of ToM impairment among brain-injured individuals, there is regionally great limitation, if none, in addressing its prevalence and its correlation with other cognitive mechanisms.

A total of 62 participants with a history of brain injury (31TBI & 31 Stroke) will be compared to a similar number of a matched, non-brain injured participants (31) on social cognitive tests, that inclusively measure cognitive and affective capacities of ToM and its correlation with brain injury outcome measure. It is anticipated that current data will reveal significant declining in both dimensions of ToM task for brain-injured sample, in compare to the matched control. It is therefore, anticipated that this effect will be mirrored by low outcome measure in socialization domain

Results demonstrated significant low score across all ToM measures for TBI & Stroke group compared to control. In addition, ToM scores were positively correlated with socialization outcome measure post brain injury which emphasize the impact on this domain. These preliminary data will assist in establishing a rehabilitation protocol limiting the vulnerability to encounter socially demanding events.

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Poster number: P-M005
Theme: Attention, motivation, behaviour

Novel zebrafish models for Autism Spectrum Disorders

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Autism spectrum disorder (ASD) is a heterogeneous psychiatric disorder characterised by deficits in communication and social interactions as well as restricted interests and repetitive behaviours. Despite research into the underlying genetics and neurobiology of ASD there are relatively few drug treatments for this disease. The aim of this project is to investigate the function of two novel ASD-candidate genes reelin and ywhaz using zebrafish as a model organism. reelin (reln) codes for a large secreted glycoprotein that is expressed in the brain and has an important role in controlling neural migration and synaptic signalling. We have observed impaired social behaviour in a reln mutant line, manifested as a reduced tendency of groups of mutant fish to shoal. To further assess the contribution of canonical reln signalling to the aetiology of ASD we will now investigate the behavioural phenotypes of vldlr and dab1a mutant lines. ywhaz is a member of the 14-3-3 family of scaffold proteins that are predominantly expressed in the adult brain. ywhaz expression is restricted to Purkinje cells in the cerebellum. Importantly, recent research has implicated the cerebellum in the pathology of ASD, with some autism patients exhibiting a reduction in number of Purkinje cells. We have generated a novel zebrafish mutant line lacking ywhaz function and will now examine its behavioural phenotype, including measurements of social behaviour and motor stereotypies. If successful, we will then use these mutants in a screen to identify novel drugs for ASD-linked behavioural alterations.

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Poster number: P-M006
Theme: Attention, motivation, behaviour

The physiological impact of distinct cholinergic populations on amygdala microcircuits and learning-related behaviour

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Both the central cholinergic system and the amygdala have long been known to be important for cognition, motivation and mnemonic processes. Different cholinergic populations innervate the amygdala but despite a strong anatomical relationship and overlap in function the precise synaptic and behavioural impact of cholinergic inputs on amygdala processes has not been thoroughly investigated. Using optogenetic-mapping strategies in transgenic ChAT-cre mice we demonstrate that amygdala-projecting basal forebrain (NBm) and brainstem cholinergic neurons can differentially impact amygdala circuits. The underlying synaptic impact of brainstem inputs to the central lateral division were excitatory, mediated solely via the synergistic glutamatergic activation of AMPA and NMDA receptors, while activating NBm to basal nucleus (BA) projections resulted in endogenous ACh release that generated a fast inhibition followed by excitation. Such a biphasic inhibitory-excitatory response profile is a

physiological hallmark of neural oscillations and could thus form the basis of acetylcholine-mediated rhythmicity in BA networks. Indeed, in vivo NBm activation strengthened NBm and BA synchrony that continued for seconds after stimulation. When photo-activated in behaving animals these differential projections resulted in opposing appetitive and aversive learning-related behavioural changes. Since learning and memory is supported by both cellular and network-level processes in central cholinergic and amygdala networks, these results provide a route by which distinct cholinergic inputs to the amygdala can aid in establishing associative biophysical modifications that underlie amygdala-dependent memories.

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Poster number: P-M007
Theme: Attention, motivation, behaviour

Nucleus accumbens, but not orbitofrontal cortex, tracks and updates cue value during probabilistic reward learning

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A critical component of adaptive behaviour is learned prediction of future rewards. While relying on frontal-striatal-dopaminergic networks, little is known about the dynamic contribution of different parts of this circuit as reward predictions are first formed. To investigate this, electrochemistry was used to measure local tissue oxygen levels – a proxy for blood oxygen level-dependent signals in fMRI – in the nucleus accumbens core (NAcC) and orbitofrontal cortex (OFC) while rats performed a probabilistic Pavlovian reward learning task. In each session, rats were randomly presented with two auditory cues (10s clicker or 10s tone), one of which had 75% reward probability (high value cue, HV) and the other 25% reward probability (low value cue, LV). Reward anticipation was assessed behaviourally by the time spent in the food magazine during cue presentation. The particular sounds used for the LV and HV cues significantly influenced the ability to learn the discrimination. To account for this, a simple reinforcement learning model including parameters for cue salience and intrinsic cue value was developed. Cue-elicited oxygen signals in both NAcC and OFC tracked learning, although the NAcC signals emerged earlier. NAc responses reflected the classic signature of a reward prediction error (RPE) as observed in fMRI studies: increased activation following unanticipated reward (LV cue trials, relative to HV), and reduced activation when reward was unexpectedly withheld (HV cue trials, relative to LV). However, it was clear that the RPEs dynamically varied across sessions, such that by the end of training there was little evidence for negative oxygen responses on trials where reward was unexpectedly omitted. In contrast to cue-related responses, RPEs were not present in OFC; activation patterns here more closely tracked the salience of the outcome for learning. Together, these findings demonstrate that NAcC and OFC play complementary but distinct roles during probabilistic reward learning. Moreover, the similarity between the RPE signals recorded here with that observed in human fMRI studies opens up opportunities to translate between dysfunctional reward-guided behaviours in neuropsychiatric disorders and the underlying neural substrates in animal models.

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Poster number: P-M008
Theme: Attention, motivation, behaviour

Tissue oxygen changes during motivated behaviour: Influence of effort, individual differences and pharmacological challenge

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Disruptions in motivated behaviours are associated with a number of neurodegenerative and neuropsychiatric disorders (Salamone et al., 2015). Motivation can be probed, across species by progressive ratio (PR) schedule of reinforcement paradigms. PR tests an organism's ability to maintain responding for reward under a progressively increasing work requirement (Hodos, 1961). The maximum ratio completed, known as breakpoint, provides a measure of effort related motivation. Drug discovery may also benefit

through the use of translational imaging during PR performance. Amperometric recording of brain tissue oxygen (O2) can be used as a surrogate of human BOLD-fMRI (Lowry et al., 2010), in awake, behaving animals. The current study therefore used O2 amperometry to probe the neural responses to reward during PR responding, both at baseline and following drug challenge.

Twelve male Wistar rats were implanted with carbon paste electrodes into the nucleus accumbens (NAc) as well as into the lateral and medial orbitofrontal cortices (mOFC/ lOFC). Changes in O2 signals following reward delivery were assessed. Under baseline conditions, there was a significantly greater NAc and mOFC O2 response to reward following trials with a higher work requirement. Additionally, animals with higher breakpoints overall showed significantly greater NAc O2 responses, than low-breakpoint animals. We then investigated the influence of clozapine administration; a drug reported to increase breakpoints (e.g. Mobini et al., 2000). Alongside increasing breakpoints, clozapine significantly increased NAc O2 responses to reward , mimicking individual differences in motivation. This study demonstrates that the use of O2 amperometry during PR performance can reveal motivationally relevant signals that may be of benefit for evaluating novel treatments .

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Poster number: P-M009
Theme: Attention, motivation, behaviour

Analysis of the interplay between brain circuit oscillations during performance in the 5CSRTT in a transgenic mouse model of Tau pathology

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Objective: Abnormal hyper-phosphorylated and mis-folded tau in the brain are prominent pathological signs associated with the disruption of on-going network activity in Alzheimer's disease (AD) that parallels cognitive deterioration. Electroencephalographic (EEG) alterations have been associated with cognitive decline in AD, including attentional processing. The present study used a transgenic tau seed injection model to investigate changes in neuronal connectivity associated with tau pathology, during attentional performance. The aim was to identify functional biomarkers of early disease progression.

Methods: 40 male P301L mice underwent surgery for electrode implantation and also a guide cannula for future injection. K18, a synthetic preformed tau fibril, or buffer control was administered into the hippocampal (HPC) CA1 region when mice were 12 weeks of age. Network oscillations in the left and right HPC CA1 regions were monitored for 20 weeks, post HPC CA1 injection, while the animals performed in the 5 Choice Serial Reaction Time Task (5CSRTT). Cross-Frequency Phase-Amplitude Coupling (CF-PAC) was used to analyse the interplay between theta and gamma oscillations.

Results: For buffer mice, pre and post injection a similar CF-PAC was visible both left and right sides of the HPC, that also correlates with a stable behavioural performance. 8 weeks post-injection, there was a decrease in CF-PAC at the injected side of the HPC and an increase in CF-PAC at the contralateral HPC. K18 injected mice show similar connectivity changes from week 4. Behavioural performance gradually decreased over time for both experimental groups.

Discussion: The mechanisms underlying CF-PAC compensation may prevent behavioural differences between K18 and buffer injected P301L mice during the 5CSRTT. The contralateral HPC may be compensating for a loss of brain activity, which may correlate to a lack of behavioural differences between the two groups. The functional changes seen within both experimental groups may be an explanation for the gradual decline in cognitive performance. The addition of the cannula may be causing inflammatory damage to the CA1 region in a time-dependent manner, also contributing to some of the functional changes seen within the EEG.

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Poster number: P-M010
Theme: Attention, motivation, behaviour

Effects of loss aversion on neural processing of choice outcomes: an event-related potential study

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Loss aversion is the tendency to prefer avoiding losses over acquiring gains of the same nominal values. Previous studies showed that loss aversion is associated with greater autonomic and cerebral responses to monetary losses compared to wins. Feedback-related negativity (FRN) is an electrophysiological response to choice outcomes, manifesting as an increased neural signal for loss compared to win feedback. The present study investigated the neural and temporal underpinnings of loss aversion and its effects on FRN amplitudes.

A monetary gambling task was used to assess loss aversion in 27 healthy participants. This task involved choices between a sure outcome and an uncertain (50% probability) gain or loss of variable amounts. Loss aversion, risk aversion and choice sensitivity were evaluated using non-linear parametric fitting of choice data. Electroencephalographic (EEG) activity was recorded continuously using a 128-channel EGI (Electrical Geodesics, Inc., USA) system. FRN was evaluated as the difference in electrical potentials between loss and win outcomes.

The amplitude of FRN in the latency interval 364-438 ms in central-parietal midline electrodes correlated with individual loss aversion values. The FRN potential was modelled by an equivalent current source dipole located in the posterior cingulate cortex (PCC); the source activity in PCC also correlated with individual loss aversion values.

Results accord previous studies demonstrating presence of a source dipole mediating FRN in PCC. PCC has been shown to participate in automatic calculation of subjective value of prospects during risky decision making. Thus, loss aversion appears to modulate the automatic valuation of outcomes by increasing the sensitivities of PCC neurons towards financial losses.

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Poster number: P-M011
Theme: Attention, motivation, behaviour

Should I trust you? Neural processing of unconscious influences on trustworthiness judgements

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The foundation of human social interactions lies in the ability to accurately decode social cues depicted on another person's face. Facial expression is highly relevant to social interaction and most importantly traits including trustworthiness of a face convey crucial social information for social exchange (Getov et al., 2015). However, research examining how affective priming may impact on trustworthiness judgements remains scarce. The current study examined the neural underpinnings of subliminal affective words on trustworthiness judgements about subsequent neutral unfamiliar faces. Twenty healthy females took part in an event-related potential (ERP) study to measure the temporal characteristics of affective priming on trustworthiness judgements. Specifically the study examined whether socially word primes induce a different effect on trustworthiness judgements than non-social ones. The manipulation of affective priming on trustworthiness judgements was evident in both behavioural and ERP results. The amplitudes of P3 and late positive potential (LPP) were greater following non-social positive primes compared to social ones. The findings reveal that: 1) there are distinct neural activation patterns between threatening and positive stimuli at 350ms post-target presentation; 2) affective priming operates relatively late during target processing; 3) trustworthiness judgements are more sensitive to the influence of positive non-social primes compared to social ones.

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Poster number: P-M012
Theme: Attention, motivation, behaviour

The role of cortex in a complex dynamic environment: a "Videogame" for rats

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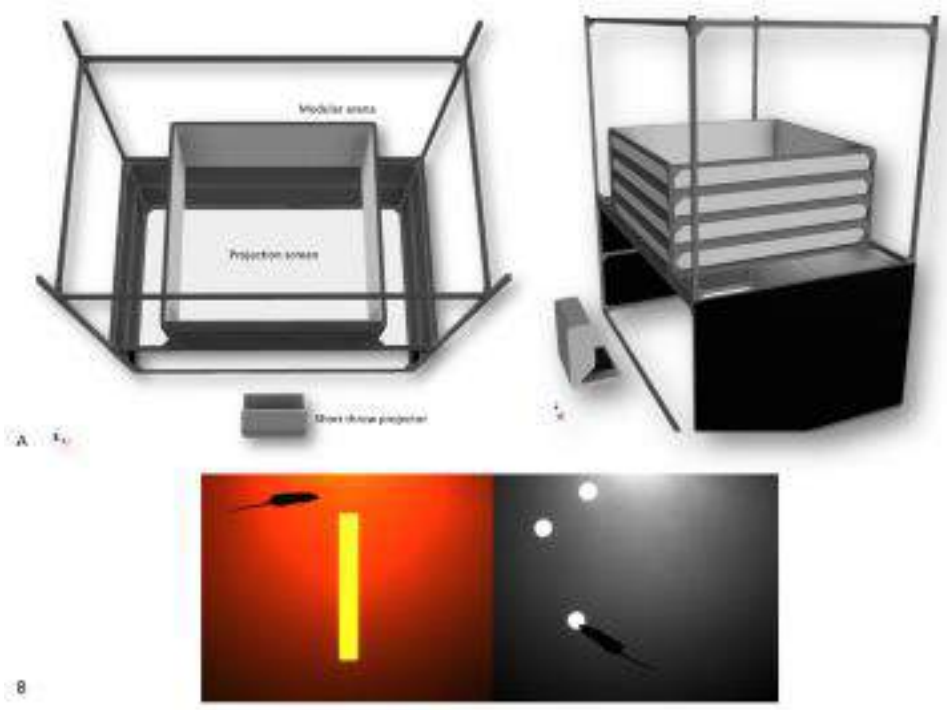
An organism's behaviour is a continuous stream of actions and reactions to the changing demands of a complex, unpredictable environment. We are able to approximate a more natural level of environment complexity with a back projection video setup that engages rats in complex visual motor tasks. Using a reactive data stream processing framework we can control, in closed-loop, most parameters of the environment in response to the animals behaviour, thus generating a rich-yet-controlled dataset for quantitative behavioural analysis. We are now characterizing the role of cortex in playing different types of "Videogames", focusing on the dorsal portion of the frontal, motor, somatosensory, parietal and visual areas (FMSPV cortex). We trained Long Evans rats in a foraging task that required them to collect projected spots of light at unpredictable times and positions. Rats quickly learned the task (less than one week) and we then performed bilateral FMSPV thermocoagulatory lesions. With this basic foraging task, lesioned rats do not show major impairments relative to shams, as they could learn and perform the task regardless of whether they had experienced it before or after lesion. This result strongly argues for increasing the complexity of the visual motor tasks in order to engage the fundamental role of FMSPV cortex, and we are now using dynamic visual stimuli that respond to the animals' behaviour. In addition to these behaviour and causality studies, we are also now monitoring distributed cortical neural activity during our "Videogame" tasks. We thus designed a novel 11 shank, 128 channel silicon probe to simultaneously record from each area (and every layer) of FMSPV cortex. This unprecedented distribution of recording sites has provided a unique picture of the cortical dynamics ongoing during complex visual motor tasks. Preliminary results from these recordings will be presented along with new behavioural data from increasingly complex task paradigms.



A. Sketches (top and side view) of the new version of the Videogame.
B. Top views of rats playing Videogames.

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Poster number: P-M013
Theme: Attention, motivation, behaviour

Modifying monkey behaviour with chemogenetic tools (DREADDs)

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Over the last decade, molecular tools have emerged as a valuable approach to asking questions in the field of systems neuroscience. Chemogenetic techniques, such as DREADDs (Designer Receptors Exclusively Activated by Designer Drugs), have been successfully used in rodents. There has been considerably less success in non-human primate (NHP) neuroscience. This is in part due to the impracticality of producing germ-line modifications in rhesus monkeys, and in part due to the cost and time required to develop effective transmission of genetic material via viral vectors. We present developments in injection technique and visualization that result in improved levels of receptor expression, allowing us to modify behaviour.

We induced high DREADD expression levels (up to 100% penetrance in a localized region) in both cortical and subcortical regions by injecting a lentivirus expressing an inhibitory DREADD, hM4Di, fused to a fluorescent reporter, CFP, expressed under a human synapsin promotor, at a titer 109 particles/L. Co-infusion with MnCl2.4H20 provided a localized MR detectable signal for ~12 hours after injection, a step that makes it straightforward to check that the viral construct was injected, and at the correct location. The developing expression can be followed by PET imaging with 11C-clozapine. By 6 weeks the expression stabilized and, using a blocking design, we were able to plot an occupancy curve for the DREADD activator, clozapine-N-oxide (CNO), showing ~70% occupancy at 10 mg/kg CNO.

Inhibitory DREADD was expressed in orbitofrontal cortex (OFC) of monkeys with a contralateral rhinal cortex (Rh) removal. When the monkey was treated with CNO (10 mg/kg i.m.), stimulus-reward association was disrupted. In a separate study, inhibitory DREADD was expressed in ventral striatum of a monkey unilaterally. Systemic CNO injection (10 mg/kg, i.m.) produced an increase in spontaneous early errors, consistent with a loss of response inhibition.

The studies performed here demonstrate that viral vector-based chemogenetic techniques can be applied to silence specific regions of NHP brain. We induced silencing of regions subserving reward valuation, thereby demonstrating the necessity of the interaction between these regions for stimulus-reward processing.

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Poster number: P-M014
Theme: Attention, motivation, behaviour

Motivational Fatigue: Quantifying how effort reduces motivation over-time in health and Parkinson's Disease

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Motivational fatigue - a reduction of motivation following effortful exertion - is a highly prevalent and debilitating non-motor symptom of Parkinson's disease (PD). Yet, little is known about its underlying mechanisms, with the majority of research using self-report approaches only. In contrast, behavioural and cognitive neuroscience frameworks characterise motivation as a series of cost-benefit decisions, where the rewards associated with acting are devalued by the effort that must be exerted. However, the willingness to exert effort is not static, it changes over-time and declines as we become increasingly fatigued due to effortful exertion.

Here, using a novel computational modeling approach on an effort-based decision-making task, we quantify the factors that influence the dynamics of motivation. Participants made choices about whether they would rather 'work' and exert a given level of effort (30-50% of their maximal grip strength) for high rewards (6-10 credits), or 'rest' and exert no effort for a low reward (1 credit). Comparing different computational models of people's choices, we identify that the willingness to exert effort is influenced by a static factor of how motivated they are to exert effort for reward generally. However, we also identified and quantified three factors (2 short-term and 1 long-term) that dynamically influence people's willingness to exert effort over time: (i) the recent

exertion of effort leads to short-term reductions in motivation, (ii) choices to rest result in short-term increases in motivation and (iii) the total amount of effort exerted during the experiment results in long-term reductions in motivation. These factors influenced most people's decisions but the extent to which they did was highly subjective. People were influenced by long-term and short-term, working and resting, to different degrees. Preliminary results of PD patients off medication, suggests that they show differences in how motivation is influenced by greater short-term effects of working and resting compared to controls. We propose that using this computational framework may provide a better understanding of the mechanisms underlying motivational impairments and the symptoms of fatigue in clinical disorders.

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Poster number: P-M015
Theme: Attention, motivation, behaviour

Determining whether animal welfare can be improved through environmental enrichment

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Animals are useful in pre-clinical research as they can be manipulated to model various neurological disorders including, for example stroke. However, such models can have a significant impact on the animal's welfare. Environmental enrichment may improve animal wellbeing by allowing species-specific natural behaviours and better environmental control. Enrichment has been shown to benefit both healthy animals and disease models by increasing neurogenesis and improving performance in memory, motor and co-ordination tasks. However, enrichment protocols vary widely and are rarely validated in terms of animal welfare. Here we aim to show that this enrichment protocol benefits rodent's wellbeing.

To assess whether healthy rodents prefer a standard or enriched housing environment, indicating improved welfare, preference tests were carried out with 10 male and 10 female C57BL6/j mice. The test consisted of a central cage with only bedding attached to two additional cages, a mouse cage with bedding, nesting material, shelter and a tube; and a larger cage with bedding, nesting material, shelter, running wheel, two tubes, tissues and lego structures. Groups of 5 mice were placed in the central cage and housed in the complex for 48 hours whilst movements were recorded. After the initial test, groups were housed in a standard or enriched environment for 39 days then completed another preference test.

The initial preference test showed both male and female mice prefer the standard environment. However, both groups spent significantly more time in the enriched cage during the dark phase compared to the light phase, so much that neither group had a cage preference during the dark phase. A preference for enrichment was observed in male mice following exposure to this cage, whilst exposure did not alter the preference of the female mice.

Exposure is required for male mice to prefer an enriched environment, suggesting that preference is impacted by familiarity and very short-term enrichment is not beneficial. Findings from females suggest that cage preference is related to nesting behaviour and not familiarity. Thus, this data identifies that wellbeing of male and female rodents are affected by different things, something which should be accounted for when housing.

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Poster number: P-M016
Theme: Attention, motivation, behaviour

Eat your Greens: Micronutrient Supplementation and Cognitive Ability in a Normative Group

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Micronutrients are required for a number of vital functions including energy metabolism and neurotransmitter synthesis within the brain (Chi & Sauve, 2013; Harrison & May, 2009). As a consequence intake insufficiency may detrimentally affect cognition. Previous research has demonstrated cognitive improvements following micronutrient supplementation in normative populations and participants with neurodegenerative disorders (e.g. dementia, multiple sclerosis) (James et al., 2013; Oudshoorn, Mattace-Raso,

Van der Velde, Colin, & Van der Cammen, 2008; Polidori & Schulz, 2014). Findings from the current research might inform future rehabilitative interventions across a range of neuropathological conditions. Participants (21-59 yrs, mean = 39.07 yrs, SD = 11.46; 75% female) were randomly assigned to three groups (multivitamin, vitamin D, vitamin C [used as placebo]; N = 60). Exclusion criteria included micronutrient supplementation over the previous month, prior head injury or neurodegenerative disease. Participants completed memory, executive function, social cognition and tacit learning measures and were randomly allocated to supplement group for an eight-week period, also completing a food diary to provide a metric of standard nutritional status. Follow up tests were administered in counterbalanced order at the end of the intervention phase. In contrast to previous research, analyses of variance found no significant differences between groups following supplementation for all measures. Diagrammatic representations comparing group performance on tasks however indicated differing changes over the study period. Therefore linear regression models were conducted to investigate if supplement levels explained these differences. These indicated that some micronutrients (particularly B vitamins) were significant predictors of score, particularly on executive function and tacit learning tasks. The identification a number of micronutrients acting as significant predictors of task performance in a normative population suggests that this model could show positive results in a head injured population, where the potential for insufficiency due to hypermetabolism and increased demand on micronutrient stores due to reparative mechanisms is higher.

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Poster number: P-M017
Theme: Attention, motivation, behaviour

Behaviour of wild-type littermates impacted by socially deficient Nlgn3 knockout mice

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In most animal species including humans, the post-natal acquisition of social behaviour critically depends on interactions with peers. Here we explore the possibility that animals carrying a mutation in a gene associated with autism spectrum disorders (ASD) impacts the development of their wild-type littermates. Genetic studies have linked NLGN3 with ASD and we found that socially deficient Nlgn3 knockout mice affect their wild type littermates' behaviour. Re-expression of Nlgn3 in parvalbumin-expressing interneurons in mutant animals rescued the behaviour of the wild-type littermates, thus further indicating that the social behaviour of mutant animals measurably impacts wild-type animals behaviour. Given the extensive use of animal models to study mutations affecting behaviour, these findings have important implications and suggest that social deficiency affecting animal behaviour may be contagious.

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Poster number: P-M018
Theme: Attention, motivation, behaviour

Linking dysregulated protein translation to specific phenotypic behaviour in the Cyfip1+/- mouse model of autism spectrum disorders

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In humans, several genes encoding for regulators of protein translation (e.g. FMR1, CYFIP1, TSC2 and eIF4E) have been associated with autism spectrum disorders (ASD). In addition, patients with Fragile X syndrome, associated to ASD, show and increased protein translation. Genetic mouse models of ASD which have contributed significantly to the molecular understanding of ASD also show a defective protein translation regulation. These results suggests the regulation of protein translation can be an important aspect of the ASD pathophysiology but, so far, little is known about the role of protein translation in specific phenotypes. To address this question we use mice heterozygous for the cytoplasmic FMR1-interacting protein 1 (Cyfip1+/-). We are testing the hypothesis that the heterozygous loss of the protein translation regulator CYFIP1 causes a dysregulation of basal protein translation which in turn gives rise to specific phenotypes. Biochemical analysis revealed a 50% decrease of CYFIP1 expression in some brain regions whereas other brain region showed expression levels similar to wild type levels. This suggests that a post-transcriptional mechanism could lead to a brain-region specific compensation of CYFIP1. We are testing this by measuring basal protein translation in vivo. Assessing the Cyfip1+/- behaviour we found a robust hypoactivity phenotype and an impaired motor learning in a Rotarod paradigm compared to wild type littermates. Motor learning requires synaptic plasticity and induces structural plasticity. Protein translation is

linked to long-term potentiation and structural plasticity relies on the synthesis of proteins as building blocks. Therefore the motor learning deficiency in Cyfip1+/- could be a consequence of a dysregulated protein translation. To better understand this relationship we aim to couple behaviour paradigms with the monitoring of protein translation in vivo.

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Poster number: P-M019
Theme: Attention, motivation, behaviour

Cortical Hyperexcitability: An underlying factor for Anomalous Perceptual Experience

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Recent work has revealed that the cortical hyperexcitation (CH) is not only found among clinical subjects such as migraineurs, but also in normal population who have either elementary or hallucinatory experience (e.g. out of body experience (OBE)). This finding has stimulated the idea that CH is correlated, or even leads, to the formation of numerous kinds of elementary and even more complex visual hallucinatory experiences. The present study attempted to test this hypothesis with a computerized behavioural task, namely Pattern glare (PG) task, and the questionnaire Cortical Hyperexcitability index – II (CHi-II). The former measures the visual discomfort on striped-patterns and the latter measures the presence of visual hallucinations and distortions, both indicating ones' CH level. Three hundred and forty-three subjects completed both tasks, and a between-subject analysis (migraineurs vs. participants who had OBE vs. control) was conducted on their responses. Results showed that subjects with migraine and OBE both had a higher score in CHi-II and a stronger PG effect in PG task than the control group. The finding is consistent with the hypothesis, and may indicate that a stronger background CH is associated with aberrant perceptual experience, which outlines a possible mechanism for the formation of visual hallucinatory experience.

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Poster number: P-M020
Theme: Sensory & motor systems

The role of nitric oxide in modulating neuronal activity in the ventral cochlear nucleus, a possible mechanism of tinnitus generation

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Tinnitus chronically affects an estimated 10-15% of adults and is characterised by the perception of sound independent of external stimuli. Nitric oxide synthase (NOS) expression has been studied in guinea pig ventral cochlear nucleus (VCN) where it is located in a sub-population of each cell type. Following unilateral acoustic over-exposure, a within-animal asymmetry of NOS expression was found exclusively in the 75% of animals that developed tinnitus (Coomber et al., 2015). The decrease in NOS expression in the contralateral VCN was observed as soon as 1 day after acoustic-over exposure, and the asymmetry in NOS expression was strongest at eight weeks after noise exposure. This provided evidence for a role of nitric oxide (NO) in tinnitus, and not simply as a biomarker for hearing loss. Here, we describe the use of iontophoresis to apply the NOS inhibitor L-NG-Nitroarginine methyl ester (L-NAME) to units within the VCN of the anaesthetised guinea pig. Upon identification and characterisation of a single unit, hour-long, pure tone pulse-trains were presented at the characteristic frequency (200 ms tone pip, 800 ms silence, 3600 repeats). The number of spikes per one second sweep were counted, allowing analysis of the changes in auditory-driven or spontaneous activity. An 80nA ejection current was applied through an iontophoresis barrel containing 50mM L-NAME during a 20 min. period starting 15 min. after the start of the pulse-train; allowing assessment of the impact of blocking NO production on identified neuronal types. Reducing NO production through NOS inhibition caused a significant increase in spontaneous and auditory-driven firing rate in 20% (2/10) of our VCN unit sample. This effect was found in both chopper and primary-like units. These results indicate that NO has a role within the VCN of reducing neuronal excitability. This effect of NO on excitability may be reversed in tinnitus animals, producing an increase in transmission with potential to contribute to the 'increased central gain' thought to be present in tinnitus animals. The next stage will involve application of L-NAME to VCN neurons in guinea pigs following noise exposure and behavioural confirmation of tinnitus, therefore allowing us to determine the functional role of NO in tinnitus.

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Poster number: P-M021
Theme: Sensory & motor systems

Different mechanisms for motor-auditory and motor-visual temporal recalibration: Evidence from transcranial direct current stimulation (tDCS)

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Sensorimotor temporal recalibration (TR) refers to the subjective temporal realignment of action and delayed feedback. Adaptation to delayed sensory feedback following an action produces a temporal compression between the action and the feedback. TR is important to maintain a relationship between causally related events by compensating for the delay. Neural mechanism underlying TR has not been fully understood. In 3 experiments employing a sensorimotor synchronization task, we investigated whether TR is a sensory modality-specific phenomenon using cathodal transcranial direct-current stimulation (tDCS). We found that cathodal tDCS over the visual cortex, and to a lesser extent over the auditory cortex, decreased visual TR. However, we did not find any measurable effects of auditory and visual cortex tDCS on auditory TR. Our study revealed different nature of TR in auditory and visual modalities. Motor-visual TR is a sensory modality-specific phenomenon, modulated by the auditory cortex. The robustness of motor-auditory TR against auditory and visual cortex stimulation suggests the dominance of the auditory modality in temporal processing. We suggest auditory modality is providing a frame of reference in the realignment of sensorimotor timing signals.

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Poster number: P-M022
Theme: Sensory & motor systems

The role of endogenous modality-specific attention in multisensory integration

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To form a solid representation of our world, the brain needs to merge signals from different senses weighted by the relative reliabilities. The extent to which these integration processes are automatic or susceptible to top-down attentional control is unclear (Tang et al., 2016). Initial evidence suggests that attention can modulate the sensory weights applied during the integration process (Odegaard et al., 2016). To evaluate the role of endogenous modality-specific attention in audio-visual (AV) integration we presented participants with synchronous auditory and visual signals that were independently sampled from four different locations in a spatial ventriloquism paradigm. In a 2 x 2 factorial design we pre-cued participants to attend to the auditory or visual modality and post-cued them to report the auditory or visual location. Our results demonstrate that the pre-cued attentional focus increased the weight of the attended sensory modality in AV integration as quantified by a stronger AV spatial bias. Additional Bayesian Causal Inference modelling (Körding et al., 2007) revealed that auditory in comparison to visual attention decreased the reliability (i.e. inverse of variance) of the visual input and increased the reliability of the auditory input. Our results suggest that modality-specific attention influences multisensory integration by enhancing the reliability of the attended sensory signal. Ongoing studies aim to determine the hierarchical level and the neural mechanisms by which attention modulates the sensory weights in the multisensory integration process (Rohe and Noppeney, 2015).

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Poster number: P-M023
Theme: Sensory & motor systems

Modelling Purkinje cell complex spike waveforms and their interactions with simple spike activity and noradrenaline in the cerebellum

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Purkinje cells are the only neuronal type to project out from the cerebellar cortex and influence downstream processing. They must therefore represent all computations performed within the cerebellar cortex. Purkinje cells fire two distinct types of action potential: simple spikes and complex spikes. Simple spikes occur at high, but variable, rates (~40Hz) and have a stereotypical waveform. In contrast, complex spikes occur relatively infrequently (~1Hz) with a variable waveform. Simple spikes and complex spikes interact within the same Purkinje cell, but it remains unknown whether variations in complex spike waveform influence simple spike activity, or vice versa. Activity from spontaneous and peripherally evoked Purkinje cells recorded in anaesthetised rats reveals that the number of spikelets generated in a complex spike positively correlates with simple spike rates before the complex spike, but after the complex spike the simple spike rate is depressed in a manner graded with spikelet number. In this way complex spikes may serve a homeostatic role, maintaining Purkinje cell simple spike activity within an operational range. Using optogenetics, in vivo complex spike waveforms were also found to be modulated by noradrenaline. When noradrenaline afferents are activated, complex spikes have narrower, faster and occasionally more spikelets. Despite the critical position of Purkinje cells in cerebellar pathways, a Purkinje cell model of complex spike waveform is lacking. A simple mathematical model of the Purkinje cell is therefore described that captures complex spike waveform dynamics and interactions with simple spiking in silico. Overall, this work suggests that differences in complex spike waveform are critical in shaping cerebellar cortical output.

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Poster number: P-M024
Theme: Sensory & motor systems

Effects of multi-gene profile on individual differences in motor adaptation: a visuomotor and force-field comparison

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Previous research has identified several dopamine-related genetic polymorphisms (i.e., COMT Val158Met, BNDF Val66Met, DRD2) that modulate the availability of dopamine in prefrontal and striatal regions, and are associated with varying levels of motor learning and performance. However, there is no evidence of the effects of these genetic differences on individual performance across different motor learning tasks. In the present study, 109 young healthy participants (mean age 19.8; 87 females; all from Caucasian/White British ancestry) learnt to adapt to a velocity-dependent force-field (Smith et al., 2006) and to a visuomotor displacement (Galea et al., 2011) in separate sessions. We quantified each participant's motor learning and retention using early and late mean performance for the visuomotor task, or a two-state space model for the force field task. We found that carriers of the low plasticity-related BDNF Met- (N=80) allele exhibited significantly lower force field learning [F(2)= 3.48, p=.034], and greater retention [F(2)= 3.37, p=.038], for the fast learning component, compared to Val/Val carriers (N=29). However, BDNF genotype did not predict performance in the visuomotor adaptation task. For visuomotor adaptation, DRD2 A1 homozygote (A1/A1) or heterozygote (A1/A2) carriers exhibited lower rates of learning compared to the A2 homozygote (A2/A2) [F(1)= 4.79, p= .031]. However, DRD2 genotype did not predict performance for the force field task. None of the tested polymorphisms explained behaviour across both tasks. Together, these results suggest that different plastic mechanisms may contribute to these two forms of motor adaptation and retention.

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Poster number: P-M025
Theme: Sensory & motor systems

High-voltage spindle oscillation episodes in the rat claustrum

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The claustrum is a thin, paired subcortical sheet of grey matter, surrounded in its central and caudal levels by the putamen and the caudate nuclei of the striatum medially and the insular cortex laterally. The claustrum has extensive reciprocal cortical and subcortical connectivity. Perhaps understandably, given the claustrum's elaborate connectome, the unanswered question of the its function has received considerable attention with an array of hypotheses posed.

Building upon one particular functional hypothesis, i.e. the 'oscillation synchrony' model of claustral function (Smythies et al., 2012), single units and LFP were recorded simultaneously from the anterior claustrum, i.e. rostral to the striatum, in unanaesthetised rats during both normal exploration and reduced wakefulness/immobilisation, i.e. putative sleep. In findings that are remarkably similar to those reported in the striatum (Berke et al., 2004), we report the presence of high-voltage spindle oscillations (HVS; 5-14 Hz), i.e. spike-and-wave discharges (SWD), in the anterior claustrum. Episodes of HVS oscillations during wakefulness occurred only during periods of immobilization, typically when the animal had fully explored it's environment. During episodes of prolonged immobilization, typically 3-5 second episodes of HVS oscillations were observed every 15-60 seconds.

During HVS episodes, a high proportion of recorded tonically active fast-firing neurons became highly phase-locked to the spike of SWD but in some units, firing was confined to the refractory wave of the SWD. In addition a high proportion of lower firing rate units, with increased latency refractory periods also become entrained to HVS oscillations, albeit with a reduced number of spikes/oscillation and these were often found to skip one or more cycles. During HVS, theta entrained units were found to exhibit either a highly reduced rate of firing during HVS or, in some cases, maintain their firing rate but change their phase. Other units that were almost silent during wakefulness became highly active during HVS oscillations while the opposite was true for others.

We propose a role for the claustrum in the regulation of sleep cycles through the selective potentiation of cortical activity.

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Poster number: P-M026
Theme: Sensory & motor systems

Visualising the timing effects of cathodal transcranial direct current stimulation on motor task performance using concurrent fMRI

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Introduction: The role of the contralesional motor cortex in stroke recovery is highly debated, but difficult to study due to heterogeneity of the clinical population. Virtual lesions created in healthy subjects using transcranial magnetic stimulation (TMS) have been suggested as an experimental model to study the contralateral cortex in the case of a disrupted primary motor cortex. However, virtual lesions created using TMS are flawed in the context of motor learning tasks involving use of the hand due to production of supra-threshold motor evoked potentials (MEPs). We wished to study the potential of cathodal transcranial direct current stimulation (tDCS) as an alternative method of inducing a down regulation of primary motor cortex to test the hypothesis that compensatory activity may occur in the contralateral M1.

Methods: We performed cathodal tDCS before and during motor task performance concurrent with functional magnetic resonance imaging (fMRI) at 3 Tesla in order to study both the neural and behavioural effects of stimulation on motor learning. 17 subjects participated in three experimental sessions (cathodal stimulation delivered prior to, and during learning, as well as a sham condition).

Results: We observed a timing specific difference in both behavioural performance and learning-related fMRI activity. Cathodal tDCS delivered prior to learning of the motor task resulted in significant slowing of response time, and an associated increase in learning-related fMRI activity in the contralateral M1.

Discussion: These results support the feasibility of using cathodal tDCS as a virtual lesion method, and also suggest that the activity seen in the contralateral M1 is associated with the change in behavioural performance.

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Poster number: P-M027
Theme: Sensory & motor systems

Genetic components in proprioceptors associated with spinal misalignment identified by muscle spindle transcriptomics

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Despite frequent suggestions that the proprioceptive system regulates spinal alignment, there is no published evidence to support this claim. Although there is a lot of physiological and anatomical information on the development of proprioceptive mechanosensors, much less is known about the genetic and molecular basis of development and function of muscle spindles. This lack of information hinders the investigation of the molecular mechanism by which the proprioceptive system may regulate spinal alignment. To overcome this obstacle, we have performed the first mapping of the transcriptome of muscle spindles. We isolated ~50 spindles from each deep masseter muscle of 3 rats, using a region of the muscle that contained few, if any, spindles as control. Utilizing the MARS-Seq method recently developed by the Amit lab (1), we successfully mapped the muscle spindle transcriptome for the first time. Preliminary analysis of the 1300 identified genes revealed many genes that are known to be highly expressed in muscle spindles, including Egr3, and Myh3. Interestingly, we also identified genes whose mutations are associated with scoliosis in humans. Our finding that genes linked to scoliosis are expressed in muscle spindles indicates this approach provides an exciting opportunity to uncover the mechanistic explanation for this proposed association.

1. Jaitin, D.A. et al. (2014) Science 343:776-779; doi:10.1126/science.1247651.

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Poster number: P-M028
Theme: Sensory & motor systems

A pilot study on the effects of cerebellar trans-cranial Direct Current Stimulation on motor network dynamics during motor adaptation in human and cat

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Recent studies of trans-cranial Direct Current Stimulation have raised the possibility that this is a relatively simple and well tolerated method that can be used as an effective therapeutic tool to treat neurological and neuropsychiatric disorders (Grimaldi et al. 2016). In particular, there is evidence that stimulation of the cerebellum (ctDCS) in humans modulates a wide range of functions, including motor learning and working memory (Grimaldi et al. 2014). Despite the increasing use of this method, it is still unclear what the underlying neurobiological basis of any effect(s) are. We have set out to measure the effects of ctDCS on the extracellular neural activity in a cat model of visuomotor (prism) adaptation, and in a standard human visuomotor paradigm. Described here are results of preliminary analysis.
Frequency-domain analysis of Local Field Potential data, simultaneously recorded in cerebellar cortex and primary motor cortex during (20 minute) ctDCS or sham stimulation of a cat, show polarity specific changes at both sites, but within different frequency bands from (0.5-250Hz). This may indicate motor network activity modulation in response to cerebellar electrical stimulation. Experiments are underway to explore the effects of ctDCS in human participants to determine if similar changes in motor network activity can be detected using EEG.

Grimaldi G. et al. (2016) Neuroscientist.
Grimaldi G. et al. (2014) Cerebellum.

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Poster number: P-M029
Theme: Sensory & motor systems

Fragile X Mental Retardation Protein controls the trafficking of Neuronal Voltage-Gated Calcium Channels

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Fragile X-associated disorders including Fragile X syndrome (FXS), the most common cause of inherited intellectual disability and autism, result from the partial or complete loss of Fragile X Mental Retardation Protein (FMRP). FMRP is an RNA-binding protein involved in the control of local translation, which has pleiotropic effects, in particular on synaptic function. We have recently described a direct interaction of FMRP with voltage-gated calcium channels ($Ca_V2.2$) that reduces cell surface expression of the channels and reduces synaptic release (Ferron et al. 2014).
Dynamic regulation of $Ca_V2.2$ channel trafficking and turnover is key to the functions of these channels in neurons. Using a $Ca_V2.2$ channel with an α-bungarotoxin binding site in an extracellular loop of the membrane protein (Cassidy et al. 2014), we are investigating the trafficking (forward trafficking and endocytosis) of $Ca_V2.2$ channels expressed in a neuronal cell line Neuro2A. Our initial data indicate that forward trafficking of $Ca_V2.2$ channels is reduced when the channel is co-expressed with FMRP.
$Ca_V2.2$ channels are critical for neurotransmission both in central neurons and in the autonomic and sensory nervous system. To test whether FMRP affects the function of $Ca_V2.2$ channel in presynaptic terminals, we monitor Ca^{2+} transients at synaptic boutons in response to stimulation using a genetically encoded Ca^{2+} indicator GCaMP6f tagged to the presynaptic protein synaptophysin (syn-GCaMP6f). Dorsal root ganglion neurons are transfected with syn-GCaMP6f together with shRNA targeting FMRP and co-cultured with dorsal horn neurons and we follow the variation of GCaMP6 fluorescence in response to electrical stimulation. Preliminary results show that Ca^{2+} influx in presynaptic terminals is increased in neurons lacking FMRP.

Our data indicate that FMRP via $Ca_V2.2$ channels is a potent regulator of presynaptic activity, and its loss is likely to contribute to synaptic dysfunction in FXS.

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Poster number: P-M030
Theme: Sensory & motor systems

Vestibular-gravitational signals influence aesthetic preferences

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The vestibular organs constantly sense linear acceleration by Earth gravity, signalling to the brain head posture with respect to gravitational acceleration. One aspect of this experience is the gravity vertical, which indicates what is up and what is down with respect to the gravitational field. Humans can accurately estimate the direction of the gravity vertical while on Earth: computing the direction of gravity is crucial for almost all successful interactions with the environment. However, little is known about whether vestibular-gravitational signals also influence aesthetic preferences.
Here we investigated whether people were more aesthetically attracted by visual vertical stimuli and whether these preferences were influenced by online vestibular-gravitational signals.

Participants used a scale to rate the attractiveness of tilted (±45° to ±5° in 5° increments) and vertical (0°) lines. Lines were displayed in front of participants in an occluded visual field. Participants were seated with their head fixed upright in a chin-rest (Experiment 1). This upright head posture was used to naturally stimulate the vestibular system in a gravity-congruent direction. Results revealed a strong aesthetic preference for vertical lines, which were rated as significantly more attractive than any of the tilted lines. Critically, roll-tilting the head 90°, and therefore leading to gravity-incongruent signals, cancelled this preference with no difference between vertical and tilted lines (Experiment 2).

Our results demonstrate a clear aesthetic preference for visual vertical stimuli. Importantly, this preference emerges only when the vestibular organs are aligned with the direction of the physical gravity vertical. Vestibular-gravitational signals may therefore play a role in aesthetic preferences, as well as basic judgements of orientation relative to gravity.

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Poster number: P-M031
Theme: Sensory & motor systems

A proposal and model of homeostatic regulation of parallel fibre activity by Golgi cells in the cerebellum: defining sparse

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Mossy fibre input to the cerebellum is received by glutamatergic granule cells whose axons (parallel fibres) are a major feature of the cerebellar circuitry, activating GABAergic Golgi cells along their course. Golgi cells in turn inhibit the mossy fibre-granule cell relay.

David Marr (1969) proposed that Golgi cells might adjust the number of inputs needed to make a granule cell fire. Under strong inhibition more inputs are necessary, with weak inhibition fewer inputs are needed. By regulating inhibition, and because not all granule cells fire that receive input, parallel fibre activity in Marr's model was a thinned out but still faithfully input specific. This was a good fit with his recoding model, which needed activity to be sparse so that pattern memories stored by Purkinje cells did not overlap and interfere with each other (Marr 1969).

It is proposed instead that granule cells fire when they receive the combination of mossy fibre input and baseline (and not elevated) Golgi cell input to what is probably either at least 2 dendrites or at least 3. Making few assumptions, this enables predictions to be tested of the effect of Golgi cell regulation of the amount of granule cell activity, using a mathematical model run in Matlab.

Among the predictions are (i) the amount of granule cell activity – the density of active parallel fibres – tends to reach equilibrium in a stable and relatively narrow range; (ii) because Golgi cell control is ubiquitous and automatic (as opposed to needing any higher or overarching logistical control) this causes parallel fibre traffic to be evenly distributed; and (iii) an effect of the action of granule cell and Golgi cell activity on each other is to confine themselves to an activity range where they have a mutual influence. Unlike Marr's hypothesis, this model predicts homeostatic regulation of parallel fibre activity, and not simply inhibitory reduction.

This has implications for recoding by the granular layer and the way the cerebellum handles information generally, and answers the question: how sparse is sparse?

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Poster number: P-M032
Theme: Sensory & motor systems

The efficient athlete brain: Cortical processing of breathlessness

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Understanding the mechanisms underlying perception of bodily sensations such as breathlessness is important for both health and disease. Endurance athletes regularly experience breathlessness, and we have shown they have closer matching between breathlessness and changes in ventilation compared with sedentary controls (Faull 2016). We have now investigated corresponding differences in brain activity when anticipating and perceiving breathlessness. We hypothesized improved efficiency in athletes (i.e. less functional activity for the same stimulus), with increases in cortical connectivity between key ventilatory control areas and attentional networks.

Forty subjects (20 athletes, 20 age/sex-matched sedentary subjects) were scanned using a 7T Siemens Magnetom (Nova Medical 32 channel Rx, single channel birdcage Tx). Anticipation and breathlessness were induced with a conditioned cue and an inspiratory resistance. Cue conditioning was conducted 15-30 hrs prior to fMRI. A resting-state scan was also acquired. T2*-weighted, gradient echo EPI (TE 24ms; TR 3s; flip angle 90; 2x2x2mm; grappa 3; 550 task volumes and 190 rest volumes) was used. Images were analysed using FEAT (FSL V.5.0). A mixed-effects analysis of group differences was performed for task fMRI. Independent component analysis (ICA) with dual regression was performed with non-parametric group comparisons on the resting state scan.

During breathlessness, athletes demonstrated less functional activity in primary sensory and motor areas. During anticipation, athletes had smaller BOLD decreases in the anterior cingulate cortex and dorsomedial prefrontal cortex; key areas of the default mode. These results imply an improved efficiency of cortical processing during breathlessness, and possibly reduced cognitive load during anticipation. Furthermore, at rest athletes demonstrated greater connectivity of a cingulo-opercular attention network to a

key area of primary motor and sensory cortices that is active during ventilatory tasks. This difference in connectivity between ventilatory and attention areas may reflect brain mechanisms underlying closer matching between ventilation and breathlessness perception in athletes.

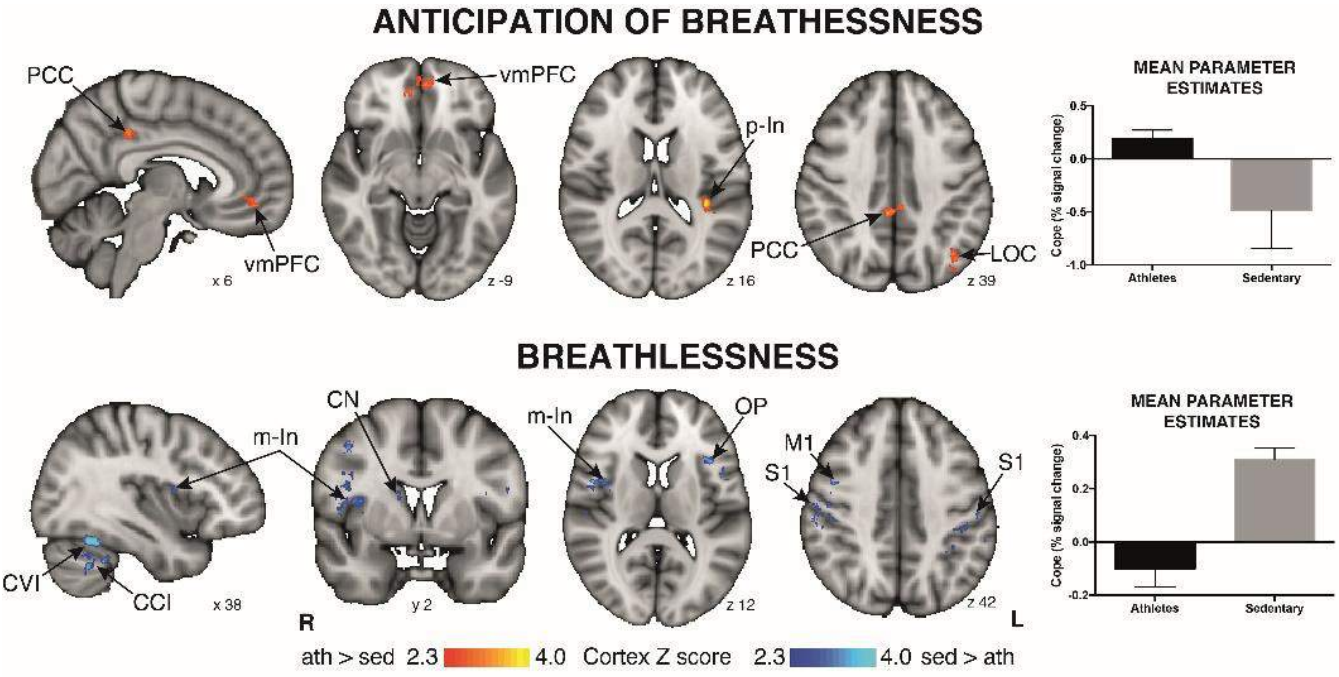

Figure 1. BOLD response differences between athletes and matched sedentary controls during anticipation of breathlessness (top) and breathlessness perception (bottom). The images consist of a colour-rendered statistical map superimposed on a standard (MNI 1x1x1mm) brain, and significant regions displayed with a threshold $Z > 2.3$, cluster probability threshold $p < 0.05$ (corrected for multiple comparisons). Abbreviations: PCC, posterior cingulate cortex; vmPFC, ventromedial prefrontal cortex; p-In, posterior insula; LOC, lateral occipital cortex; m-In, middle insula; CN, caudate nucleus; OP, opercular cortex; M1, primary motor cortex; S1, primary sensory cortex; CCI, cerebellar crus I; CVI, cerebellar VI. Right: Mean parameter estimates across a mask of statistically significant areas, for visualisation.

Faull OK, Cox PJ & Pattinson KT, 2016. Frontiers in Physiology, 7

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Poster number: P-M033
Theme: Sensory & motor systems

The intergeniculate leaflet directly modulates circadian entrainment

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The master biological clock, i.e. the suprachiasmatic nucleus (SCN) of the anterior hypothalamus provides individuals with the ability to predict the timing of circadian events and to adjust physiological processes accordingly. The evolutionary advantage of a biological clock rests on its predictive power, but adaptability to environmental changes is also important. Light is the principal zeitgeber of the mammalian circadian system and SCN neurons react to changes in the light/dark cycle by re-entraining their circadian oscillation. Accordingly, the SCN receives direct photic information from the retina via the retino-hypothalamic tract. The intergeniculate leaflet (IGL) of the thalamus seems to be, besides the SCN, another important neural structure in the mammalian circadian time-keeping system. The IGL is also densely innervated by the retina, and projects to the SCN. However, its role in mediating circadian entrainment remains somewhat elusive.

By using a new genetic mouse line (Sox14Cre) we selectively manipulate thalamic neurons that project to the SCN to investigate their ability to modulate circadian behaviour. We optogenetically stimulated IGL neurons in vivo over multiple days at different circadian times, and we showed that this specific subset of neurons was sufficient to phase-shift daily activity rhythms. Subsequently, we mapped the inputs to the IGL from the retina and other brain regions using mono-synaptic restricted ΔG-rabies virus strategy. We demonstrated that different subtypes of photosensitive retinal ganglion cells (pRGCs) innervated the SCN and the IGL and that several neuromodulatory systems converged onto the IGL.

Overall, our data suggest that the IGL is sufficient to regulate circadian entrainment of the SCN. Its function may thus consist in integrating light information with other relevant cues to adjust the phase of daily activity and to adapt it to environmental parameters.

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Poster number: P-M034
Theme: Sensory & motor systems

The invisible ventriloquist – can unaware flashes alter sound perception?

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Information integration across the senses is fundamental for effective interactions with our environment. A controversial question is whether signals from different senses can interact in the absence of awareness. Models of global workspace would predict that unaware signals are confined to processing in low level sensory areas and thereby prevented from interacting with signals from other senses in higher order association areas. Yet, accumulating evidence suggests that multisensory interactions can emerge –at least to some extent- already at the primary cortical level [1]. These low level interactions may thus potentially mediate interactions between sensory signals in the absence of awareness.

Combining the spatial ventriloquist illusion and dynamic continuous flash suppression (dCSF) [2] we investigated whether visual signals that observers did not consciously perceive can influence spatial perception of sounds. Importantly, dCFS obliterated visual awareness only on a fraction of trials allowing us to compare spatial ventriloquism for physically identical flashes that were judged visible or invisible.

Our results show a stronger ventriloquist effect for visible than invisible flashes. Yet, a robust ventriloquist effect also emerged for flashes judged invisible. This ventriloquist effect for invisible flashes was even preserved in participants that were not better than chance when locating flashes they judged 'invisible'.

Collectively, our findings demonstrate that physically identical visual signals influence the perceived location of concurrent sounds depending on their subjective visibility. Even visual signals that participants are not aware of can alter sound perception. These results suggest that audiovisual signals are integrated into spatial representations to some extent in the absence of perceptual awareness.

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2. Maruya, K., Watanabe, H. & Watanabe, M. Adaptation to invisible motion results in low-level but not high-level aftereffects. J. Vis. 8, 1–11 (2008).

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Poster number: P-M035
Theme: Sensory & motor systems

Clustering of subthalamic nucleus 20-30 Hz beta oscillations after contralateral footsteps is enhanced with auditory cues

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About half of all patients with Parkinson's disease suffer from intermittent freezing of gait (FOG), which can cause falls and thus poses a major risk to the well-being of patients (1). In many cases these motor blocks are unresponsive to medication or deep brain stimulation therapy. We set out to answer if activities in the left and right subthalamic nucleus (STN) are modulated by gait, and if so, whether in unison or in an opposing manner. As rhythmic auditory cues can improve gait rhythmicity as well as FOG (2), we also tested how any modulation changes when auditory cues are provided.

We recorded local field potentials from the STN in 9 Parkinson's disease patients during stepping in place on a foot pedal. Patients sat on a chair to avoid falls and movement artefacts. The constant step interval of 1s was set by the timing of heel strikes displayed by a looped video of a walking man. In 7 of the 9 patients, we also provided a metronome sound synchronised with each heel strike in half of the stepping sequences.

We found that high beta oscillations (20-30 Hz) were most likely to occur after the contralateral step, when the contralateral foot rested on the pedal. After the ipsilateral step, when the contralateral foot had to be raised, beta oscillations were least likely. Power in the left and right STN, particularly in the 20-30 Hz beta band, was thus modulated separately in opposite patterns.

The metronome improved patients' synchrony with the heelstrikes displayed in the video and also increased beta modulation. Our results raise the possibility that alternating DBS patterns may provide better control of gait than constant stimulation of both STN.

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2. Arias P, Cudeiro J. Effect of rhythmic auditory stimulation on gait in parkinsonian patients with and without freezing of Gait. PLoS One. 2010;5(3).

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Poster number: P-M036
Theme: Sensory & motor systems

Mapping somatomotor and cognitive function in the human cerebellum

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Animal studies have demonstrated somatotopically organised sensory and motor maps within the cerebellum, but human experimental and clinical data suggest additional involvement in cognitive functions. This study mapped sensorimotor, verbal working memory, speech motor and language functions in the cerebellum. Twenty healthy adults underwent cerebellar optimised fMRI in a 3T scanner with 4 paradigms: 1) motor: moving right fingers or toes at visually paced irregular rhythm; 2) sensory: vibrotactile stimuli delivered to the right index finger, first toe or both; 3) language and speech motor: in response to aurally presented stimuli (nouns) subjects generated associated verbs (aloud or subvocally), repeated non-words aloud, or listened to nouns and non-words; 4) verbal working memory: using the Sternberg task. Following field-map unwarping and physiological noise correction, individual responses were estimated. Group activity was assessed with a mixed effects model in FSL software, with cluster forming threshold $Z>3.09$ and corrected significance level of $P<0.05$ for the motor, language and Sternberg paradigms. Dual representation was observed in the cerebellum for the motor paradigm, with finger and toe movements producing activity in the right hemisphere ipsilateral to the task, in lobules V and VIII (fingers) and lobules I-IV and VIIb-VIIIa (toes). Finger and toe areas for the sensory paradigm overlapped with the corresponding motor map in the anterior lobe (uncorrected, $p<0.005$). Speech motor results showed bilateral activation in both superior and inferior cerebellum with the activation in the anterior lobe positioned adjacent and caudal to the finger sensorimotor area. The language paradigm showed a right lateralised activity in lobule VI, Crus I and II superiorly and in lobule VIIb inferiorly. During the encoding phase of memory paradigm, load dependent BOLD activity was observed in right lobule VI, Crus II and VIIb and vermis VI. When the presented letters¬ were held in memory, the largest area of BOLD activation was observed in lobule VI, extending into Crus I bilaterally as memory load increased.The range of tasks probing cerebellar activity associated with sensorimotor and higher order tasks demonstrated a clear spatial compartmentalization of function.

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Poster number: P-M037
Theme: Sensory & motor systems

Whisker movements in the 5XFAD mouse model of Alzheimer's Disease are affected by gender and retinal degeneration

Authors: Robyn A Grant - *Biology Manchester Metropolitan University*, Richard E Brown - *Psychology & Neuroscience Dalhousie University*

Active whisking in mice and rats is one of the fastest behaviours known to mammals and is used to guide complex behaviours such as exploration and navigation. During object contact, whisker movements are actively controlled and undergo robust changes in timing, speed and position. This study focuses on characterising whisker movements in male and female 5XFAD mice, a model of Alzheimer's disease, and their WT controls, in a number of different tasks, including object exploration, tunnel running and novel object exploration. As a result of genes from the background strains, some mice had retinal degeneration (RD). Forty-nine 6-7 month old mice were filmed behaving freely in an open field containing an object, under infrared light using a high-speed video camera at 500fps. Whiskers were tracked and variables, such as position, amplitude, speed and asymmetry, were extracted and compared pre-contact and during contact. Measuring whisker movements in these animals presents a quantitative way to capture exploratory behaviours. The transgenic mice had significantly altered whisker angular positions, amplitude and asymmetry during contact; and female 5XFAD mice with RD had lower mean angular positions during contact. Differences due to gender and RD were found in the data, with female mice making larger and faster whisker movements overall, and mice with RD making larger and faster whisker movements during contact. The data shows that measuring whisker movements can quantify the effects of the Alzheimer's transgenes, sex differences and the problem of retinal degeneration on exploratory behaviour in these mice.

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Poster number: P-M038
Theme: Sensory & motor systems

Neuronal and Metabolic Origins of Negative BOLD Within and Across Sensory Cortices: An EEG-fMRI Investigation

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Background
Sensory stimulation evokes negative BOLD responses (NBRs: signal decrease relative to baseline), both intra-modally (IM, in stimulated sensory cortex) and cross-modally (CM, in other sensory cortices). However, despite regular observation, these NBRs remain poorly understood. Here we used multimodal neuroimaging to investigate whether: 1) IM and CM NBRs exhibit similar underlying changes in neuronal activity and metabolism; 2) IM and CM NBRs are modulated similarly by stimulus intensity.

Methods
EEG, BOLD and CBF responses were simultaneously recorded in 17 subjects at 3T. 24 trials of four tasks were performed (14/20s on/off): viewing 100% or 10% contrast left-hemifield visual reversing checkerboards (3Hz), complex finger-tapping or simple handgrip motor task (right-hand).
Beamformer analysis localised changes in alpha (α) and beta (β) EEG oscillatory power between stimulation and rest. IM and CM EEG responses were extracted from virtual electrodes (VE in visual (V1) and motor (M1)) cortex and single-trial responses measured. GLM analyses localised: 1) main effect BOLD and CBF responses and also trial-by-trial fMRI correlations with 2) α- and 3) β-response variability. Metabolic demand (CMRO2) was calculated at peak regions.

Results
IM and CM NBRs were evoked by both visual and motor tasks. NBRs and negative CBF responses were spatially coincident (Fig A&B). Increased visual contrast and motor task difficulty led to increased magnitude and extent of both IM and CM negative fMRI responses (Fig A&B). CMRO2/CBF ratio was significantly higher for IM NBRs than PBRs or CM NBRs (Fig C&D).
Close links between α&β responses and both IM and CM NBRs shown by EEG-fMRI correlations: positive during visual trials, contralateral M1 with the IM VE; negative during motor trials, contralateral V1 with the CM VE.

Conclusion
IM NBR regions coincide with α&β desynchronization whereas CM NBR regions show little group EEG response. Both IM and CM NBR show decreases in CMRO2, are modulated by stimulus intensity, correlate with α&β responses. These results support a neuronal origin of IM and CM NBR, possibly reflecting regional suppression during the task.
Future work: examine between-subject variability between α&β-fMRI responses in NBR regions.

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Poster number: P-M039
Theme: Sensory & motor systems

Investigating the stability of cerebellar transcranial direct current stimulation (tDCS) effect during visuomotor adaptation tasks

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Background
Sensory stimulation evokes negative BOLD responses (NBRs: signal decrease relative to baseline), both intra-modally (IM, in stimulated sensory cortex) and cross-modally (CM, in other sensory cortices). However, despite regular observation, these NBRs remain poorly understood. Here we used multimodal neuroimaging to investigate whether: 1) IM and CM NBRs exhibit similar underlying changes in neuronal activity and metabolism; 2) IM and CM NBRs are modulated similarly by stimulus intensity.

Methods
EEG, BOLD and CBF responses were simultaneously recorded in 17 subjects at 3T. 24 trials of four tasks were performed (14/20s on/off): viewing 100% or 10% contrast left-hemifield visual reversing checkerboards (3Hz), complex finger-tapping or simple handgrip motor task (right-hand).
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Conclusion
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Future work: examine between-subject variability between α&β-fMRI responses in NBR regions.

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Poster number: P-M040
Theme: The neurobiology of stress

Effects of venlafaxine on behavior, monoaminergic and immunity parameters in female mice subjected to chronic social instability stress

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Women are twice as likely as men to develop stress related disorders such as depression, being the population that receives antidepressant treatment more frequently. This sexual disparity is also observable in effectiveness of treatments. Despite this fact, most of studies that have used animal models for determinate the physiological mechanisms implicated in depression and to develop specific drugs for their treatment have been performed in males. The aim of this study was to analyze the effects of chronic social stress on the anhedonic behavior, immunity parameters and central monoaminergic activity in female mice. We also studied, if the treatment with venlafaxine, an ISNSR, reverses these effects. For this purpose, CD-1 female mice were subjected to social chronic instability stress for 7 weeks, and they were administered venlafaxine (20 mg/kg, ip) during the last 3 weeks of stress period. The behavioral results indicate that stressed mice consumed less sucrose solution than control mice, which is associated with depressive-like behavior. Furthermore, different changes were observed in the monoaminergic activity depending of brain structure analyzed. Thus, stress produced an increase in serotonergic activity in PFC, but not in HC, where stressed mice showed lower levels of 5-HIAA and 5-HT. In PFC, stressed mice showed lower levels of 3-HK and a lower ratio of KYN/5-HT in HC. Stressed mice showed lower levels of MHPG and NE in PCF and HC, respectively, suggesting a decreased noradrenergic activity in both structures. Likewise, the greater weight of the spleen in stressed mice suggests an increase of the immune activity in this group. Venlafaxine treatment did not produce strong changes, but it reversed the effects of stress on 3-HK levels in PFC and increased 5-HIAA and DOPAC levels in this structure. Results indicate that in female mice this stress model produce behavioral and immunitary disturbances, as well as changes in several monoaminergic metabolic pathways, which are partially reversed by venlafaxine. In sum, these results suggested that further studies would be necessary for greater knowledge of biomarkers implicated in stress related disorders in females that contribute to the development of more specific pharmacological treatments.
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Poster number: P-M041
Theme: The neurobiology of stress

Revisiting the cross-stressor adaptation hypothesis: effects of ageing and aerobic fitness on stress reactivity

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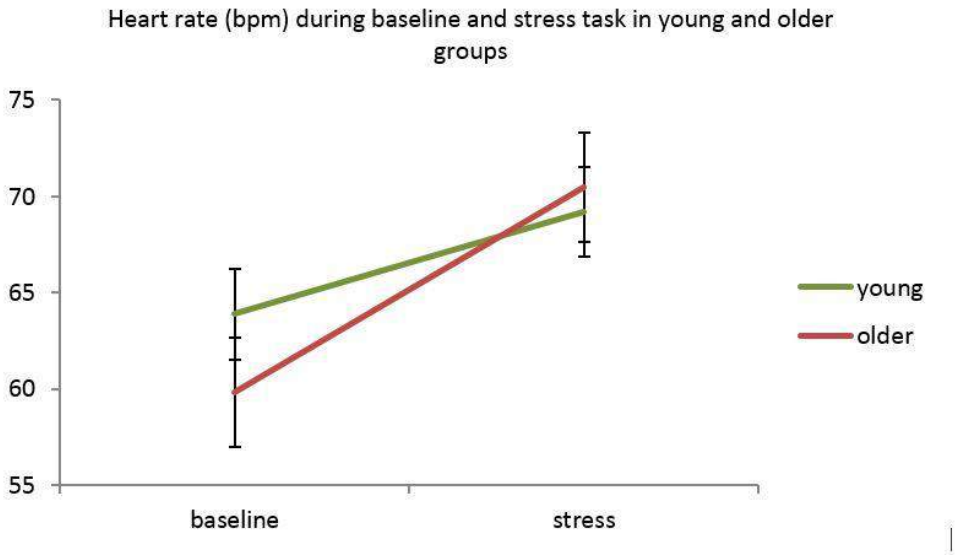
The cross-stressor adaptation hypothesis proposes that aerobic fitness leads to a decreased physiological response to exercise and psychological stress (Sothmann et al., 1996). However, others argue that exaggerated physiological responses to psychological stressors are not metabolically coupled (i.e. evoke blood pressure (BP) and heart rate (HR) increases without a concomitant increase in oxygen consumption) (Turner and Carroll, 1987). Thus fitness may not necessarily translate to adaptations to psychological stress even if it reduces responses to exercise stress. PURPOSE: The aim of this cross sectional study was to investigate cardiovascular responses in young and older, fit and unfit individuals at rest and during acute psychological stress. METHODS: Thirty 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; 68 ± 3 yrs; 6 fit, 6 unfit; VO2max >30 mL·kg·min-1 vs. <20 mL·kg·min-1) participated. During separate visits they completed an aerobic fitness test (VO2 max) and a paced auditory serial addition task (PASAT). RESULTS: Between group ANOVAs revealed a significant interaction between time (baseline and stress task) and age group on HR (p=.028), such that older individuals showed a greater change from baseline to stress. However, there were no differences in the response to stress between fit and unfit individuals (BP: p= .292; HR: p= .609). Nonetheless, the number of correct mental arithmetic responses was significantly higher in the older fit group than the older unfit group (p=.004). CONCLUSION: Fitness had no effect on BP or HR changes in response to psychological stress in either age group, but older fit individuals performed better at the mental arithmetic stress despite having a similar physiological response to the unfit group. These findings indicate that fitness does not result in adapted physiological responses to psychological stress, but may impact on behavioural engagement with psychological challenges and thus cognitive performance.



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Poster number: P-M042
Theme: The neurobiology of stress

How does stress affect cerebellar-dependent saccadic adaptation and how does this compare to polarity-dependent tDCS? A Proof-of-Principle-Study

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Differences in cerebellar structure and function are consistently reported in individuals exposed to early-life stress and individuals with diagnosed stress-related psychopathology. Saccadic adaptation is a cerebellar-dependent mechanism that restores the accuracy of saccadic eye movements, following repeated errors. It is currently unknown whether and how saccadic adaptation could be affected by stress. Recent studies have demonstrated that transcranial direct current stimulation (tDCS) over the cerebellum can either increase or decrease sensorimotor adaptation, probably via excitation or inhibition of the cerebellum. Consequently, the aim of this study was to investigate the effects of experimentally-induced acute stress on saccadic adaptation and to demonstrate how this would relate to either anodal or cathodal tDCS. Saccadic adaptation was elicited using the double-step target paradigm in young healthy men and women. In this paradigm, target position is manipulated to artificially induce a saccadic error, which subsequently aims to restore accuracy by progressively increasing saccade size. Saliva for cortisol determination and subjective measures of stress were collected repeatedly. In the first experiment, 49 participants were exposed to either a stress or a control condition using the offline version of the Montreal Imaging Stress Task (MIST), shown to generate significant physiological responses. Adaptation was assessed 10 minutes after stress induction, when cortisol levels peaked. Participants in the stress group reported significantly more stress symptoms than controls and did not demonstrate a significant increase of saccade size compared to the control group. In the second experiment, 46 participants underwent 15 minutes of anodal, cathodal, or sham tDCS whilst performing the same adaptation task. Preliminary results showed that anodal stimulation tended to increase the extent of saccadic adaptation. Conversely, participants exposed to cathodal stimulation did not show a significant increase of saccade size. Taken together, these results suggest that acute stress reduces the ability to acquire saccadic adaptation potentially via a decrease in cerebellar excitability.

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Poster number: P-M043
Theme: The neurobiology of stress

The avian hippocampus is sensitive to chronic stress at the caudal pole

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Levels of adult hippocampal neurogenesis (AHN) integrate experiences in a valence-specific manner and may present an objective marker of welfare. In rodents, AHN is suppressed by cumulative chronic stress, whilst being increased by experiences associated with improved mood, such as exercise, environmental enrichment and antidepressant treatment. These responses are largely restricted to the ventral hippocampus, which coordinates emotional behaviours and provides negative feedback to the HPA stress-axis, whilst the dorsal region is involved in spatial memory and cognition. For anatomical reasons, we hypothesised that the caudal pole of the avian hippocampus is homologous to the stress-responsive ventral region in mammals and therefore our primary aim was to test whether AHN in the caudal hippocampus in poultry is sensitive to cumulative chronic stress.

Tissue was obtained from 64 HyLine Brown hens (aged 18-26 weeks during study) which were exposed to randomized and unpredictable stressors over an 8 week period. As expression of the protein doublecortin (DCX) provides a marker of immature neurons arising from AHN, we used immunohistochemistry to stain DCX-positive cell bodies, which were quantified via stereological cell counts.

Whilst the density of DCX-expressing multipolar neurons did not differ between hens exposed to chronic stress and control birds in the rostral hippocampus ($\chi 21 = .173$, $p = .677$), stressed-birds exhibited significantly fewer DCX+ multipolar neurons at the caudal pole ($\chi 21 = 4.25$, $p = .039$); indicating a suppression of AHN under stress specific to this subregion. In order to validate this finding and assess its amenability to measurement via the quicker method of real-time PCR, we are currently using this technique to compare the expression of DCX mRNA in hens which were housed in either a preferred (high welfare) or non-preferred (low welfare) environment. Comparison between DCX mRNA levels in the rostral and caudal hippocampi of birds with these two classes of cumulative experience will be presented at the meeting.

We conclude that the caudal end of the avian hippocampus is sensitive to chronic stress. Thus, measuring AHN in the caudal hippocampus post-mortem may provide an objective marker of the cumulative welfare state of poultry.

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Poster number: P-M044
Theme: The neurobiology of stress

Investigating the effect of a model of liver fibrosis on affective state in mice

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Introduction: Modelling chronic disease in mice is essential to further our understanding of disease aetiology and for developing treatments. However, mice models of chronic disease may suffer discomfort or pain due to the nature of disease or experimental procedures. To understand the impact that chronic disease has on the welfare of mice, it is necessary to quantify an animal's affective state. Physiological markers of stress can provide a useful proxy measure for affective state. In particular, the birth of new neurons within the dentate gyrus of the hippocampus, adult hippocampal neurogenesis (AHN), is a process that is responsive to an animal's cumulative experience. Increases in AHN are correlated with positive experiences (e.g. environmental enrichment), whereas decreases in AHN are correlated with negative experiences (e.g. unpredictable chronic mild stress). Changes in AHN also show functional specificity within the dorsal and ventral regions of the hippocampus. Whereas the dorsal region primarily serves cognitive-related behaviour and memory, the ventral region is primarily associated with mood-related behaviours. Measuring AHN within the ventral hippocampus may therefore be a suitable tool to assess the impact of chronic disease on the welfare of mice. AHN can be quantified by measuring the expression of doublecortin, a microtubule binding protein that is a marker for immature neurons within the granule cell layer of the dentate gyrus.

Aims: This project aims to determine the impact of a model of liver fibrosis on affective state in mice.

Methods: Male cRel fl/fl mice were injected bi-weekly with CCl4 for 8 weeks to induce liver fibrosis . Mice in the control condition were injected with olive oil bi-weekly for 8 weeks. Open-field tests were conducted to assess depressive-like behaviour. From all mice, the dorsal and ventral hippocampus from one hemisphere was processed to quantify doublecortin mRNA expression using real-time PCR. The other hemisphere was processed to quantify doublecortin protein expression using immunohistochemistry.

Results: This poster will present the current findings of the project.

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Poster number: P-M045
Theme: The neurobiology of stress

Role of nitrergic neurotransmission in the dorsal hippocampus on cardiovascular control in isolated rats

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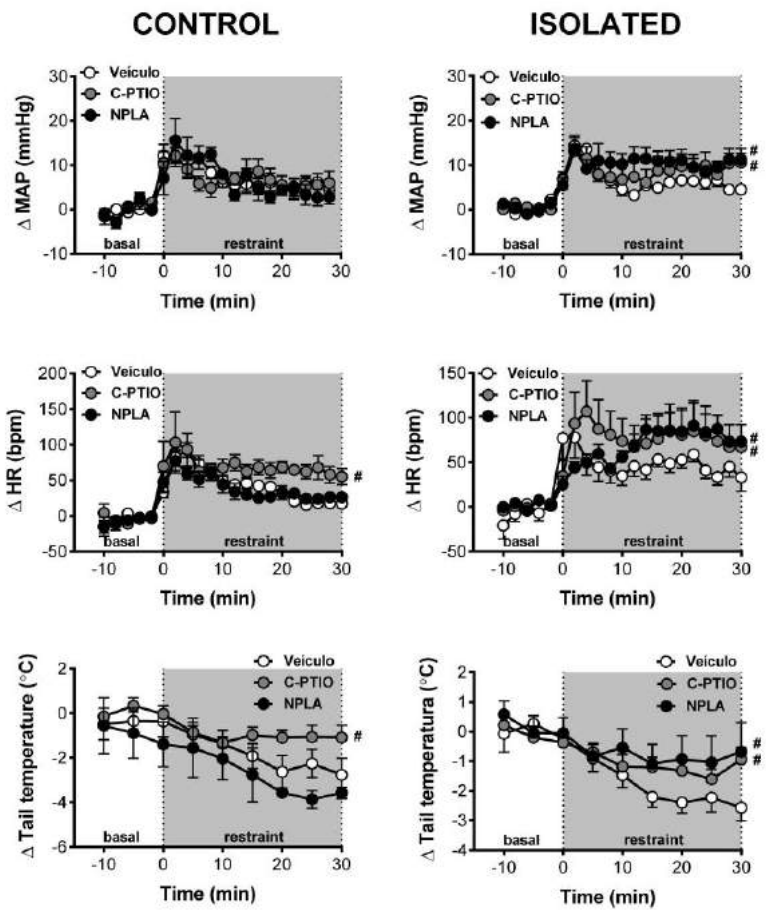
The aim was to investigate the influence of social isolation in the modulation of cardiovascular responses to acute restraint stress by nitrergic neurotransmission in the dorsal hippocampus in rats. For this, twenty-one days old male Wistar rats were divided into 6 groups (n=6/group): control (vehicle), control (NPLA), control (C-PTIO), isolated (vehicle), isolated (NPLA) and isolated (C-PTIO). Isolated rats were housed individually for 5 weeks. On the 35th day, animals underwent stereotactic surgery for implantation of guide cannulas into the dorsal hippocampus, and 72 hours later a catheter was implanted into the femoral artery for cardiovascular recording which was performed 24 hours after surgery. On the trial day, the animals received bilateral microinjection into the dorsal hippocampus of NPLA (0.1nmol/500nL, selective nNOS inhibitor), carboxy-PTIO (2nmol/500nL, NO scavenger) or vehicle (saline, 500nL). Ten minutes after treatment all animals underwent a 30-minute session of restraint stress. Neither social isolation nor dorsal hippocampus treatment with NPLA ($P>0.05$) or C-PTIO ($P>0.05$) affected basal values of either arterial pressure and heart rate. Microinjection of C-PTIO in control animals enhanced restraint-evoked tachycardia ($P<0.0001$) and decreased the drop in tail skin temperature ($P<0.0001$). Moreover, hippocampus treatment of isolated animals with either NPLA or C-PTIO enhanced the tachycardiac ($P<0.0003$) and pressor ($P<0.0002$) responses and decreased the drop in skin temperature ($P<0.01$) evoked by restraint stress. Current findings indicate that social isolation triggers the release of nitric oxide by nNOS within the dorsal hippocampus during stress. The nNOS-derived nitric oxide within the dorsal hippocampus of isolated animals plays an inhibitory role on blood pressure and heart rate increases and facilitate the sympathetic-mediated cutaneous vasoconstriction to stress.

Financial support: CNPq and PADC-FCF/UNESP.



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Poster number: P-M046
Theme: The neurobiology of stress

Intrinsic properties of central amygdala dynorphin neurons

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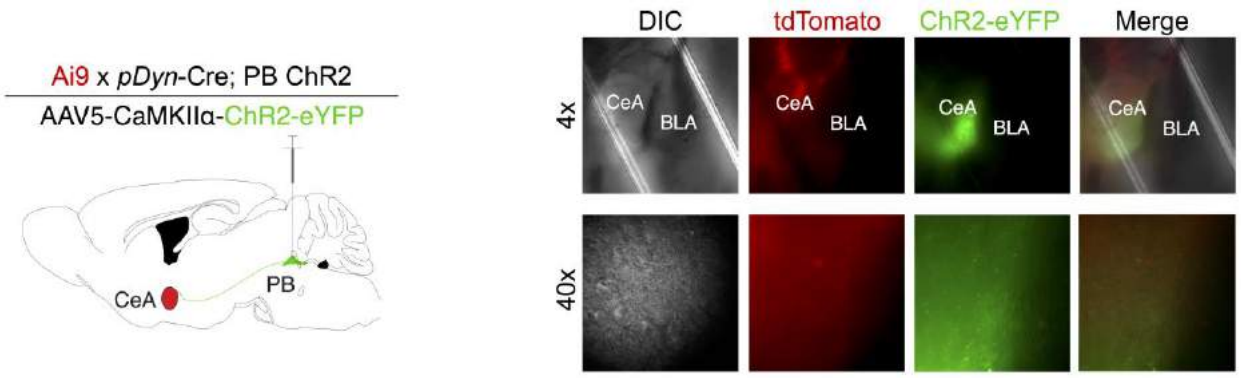
The central amygdala (CeA) is a critical anatomical substrate for emotional regulation in response to stress, pain, and alcohol-related behaviors. While many cell-types have been identified in the CeA, much less is understood about the unique properties of these molecularly-defined neurons. We focus on a subset of neurons in the CeA expressing the neuropeptide dynorphin (Dyn+), the endogenous ligand of the kappa opioid receptor. To genetically identify dynorphinergic (Dyn) neurons, we crossed a Cre-dependent tdTomato reporter mouse to a mouse expressing Cre recombinase under the same promoter as preprodynorphin. In this model, only dynorphinergic cells express tdTomato, allowing complete visualization of dynorphinergic circuitry throughout the brain and visually-guided, targeted whole-cell recordings in amygdala slices. We report distinct patterns of c-fos expression in these neurons following stress, pain, and alcohol exposure. We also document the intrinsic electrophysiological properties of these neurons and the strengths of inputs they receive from the parabrachial nucleus and the basolateral amygdala. Furthermore, the morphology of CeA Dyn+ neurons is defined by filling the cells with Neurobiotin. To determine the long-range connectivity of Dyn+ CeA neurons, we utilized cell-type selective expression of reporter viruses to identify these molecularly-defined projections throughout the brain. Together these data provide a base knowledge for further cell-type selective manipulation and observation in vivo. Understanding the mechanisms by which the dynorphin/kappa opioid system regulates emotional processing in the context of stress, chronic pain, and alcohol abuse will provide valuable insight into potential therapeutic targets for these neurological and neuropsychiatric disorders.



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Poster number: P-M047
Theme: The neurobiology of stress

Chronic variable stress reduces expression of corticotropin-releasing factor (CRF) receptors in the bed nucleus of stria terminalis (BNST) in rats

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INTRODUCTION: Stress is proposed to be involved in etiology of several diseases. Chronic stressors cause morphological and neurochemical changes in the bed nucleus of stria terminalis (BNST). Corticotropin-releasing factor (CRF) in the BNST has been implicated in control of stress-related behavioral and physiological responses. However, neuroplasticity in this neurochemical mechanism following exposure to chronic stressors has never been evaluated. Therefore, we investigated the expression of both CRF1 and CRF2 receptors in the BNST following exposure to a protocol of chronic variable stress (CVS) in rats. METHODS: The CVS protocol consisted of exposure to different stressors in variable schedules for 10 consecutive days. Twenty-four hours after the last session of stress, the animals were sacrificed and the brain were removed and stocked into a freezer in -80°C. Afterward, the BNST of all groups were collected by microdissection and protein levels of both CRF1 and CRF2 receptors were analyzed through Western-Blotting technique. Data were expressed as percentage of the control group values. RESULTS: The rats chronically stressed exhibited reduction in expression of both CRF1 (59±9 vs 100±13, t=2.4; P<0.03) and CRF2 (46±6 vs 100±15, t=2.9; P<0.01) receptors within the BNST. CONCLUSION: Chronic stress reduces expression of CRF receptors in the BNST, which can be related with stress-evoked diseases.

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Poster number: P-M048
Theme: The neurobiology of stress

Time course evaluation of the behavioral consequences generated by electrical stimulation of the dPAG of rats using the elevated plus maze

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The periaqueductal gray matter (dPAG) is involved in coordinating aspects of the fear responses. The dPAG-electrical stimulation (ES) produces a defensive reaction characterized by freezing, escape and autonomic reactions. The main interest in studying these responses are based on clinical findings which suggest that these fear responses are related to panic disorder. There are two types of freezing associated with dPAG: the freezing directly produced by dPAG-ES and the dPAG post-ES. While the former is a preparatory response to the escape, the second reflects a transfer process of information to forebrain structures, which allows the animal to assess the consequences of the aversive situation and to recognize the threatening stimulus. Some findings pointed to the role of Substance P by NK1 receptors in the amygdala in the evaluation of these aversive consequences generated by dPAG-ES. However, the time course of these consequences is still unknown. The exploratory behavior of independent groups of rats treated with Spantide (SPA, NK1 antagonist) in the central nucleus of the amygdala in the dPAG-ES day was valued in the elevated plus maze (EPM) at 1, 7 and 14 days later. The results showed that the control rats reduced the frequency of entries and time spent in the

open arms of the EPM in all intervals analyzed, while SPA treatment minimized these consequences only in the 1 day interval group. Together, these findings show that the effects of dPAG-ES are long-lasting and modulated by NK1 receptors. It suggests that the aversive information generated in dPAG is sent to rostral brain structures involved in the evaluation and recollection of the stressor, and do not result only in a motor output of defensive reaction as they have been currently thought.

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Poster number: P-M049
Theme: The neurobiology of stress

HIPPOCAMPAL MONOAMINERGIC CHANGES ACCORDING TO STRESS COPING STRATEGIES IN TUMOR INOCULATED MICE

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Depression is associated with both, cancer disease and social stress, being of special relevance the way in which people deal with stress. Although mechanisms underlying this relation are still inconclusive, it is known that stress and tumor are related to increased inflammatory markers which activate tryptophan metabolic pathway towards kynurenine production. This activation can result in a rise of 3- hidroxikynurenine (3-HK) and neurotoxic products that affect cerebral activity, and hence contribute to depressive-like behaviour. Therefore, this study aims to analyse the effects of stress coping strategies on hippocampal tryptophan metabolic pathway activity in tumor inoculated mice.

For this purpose, OF1 male mice were inoculated with B16F10 melanoma tumor cells. A subgroup was exposed to social stress, using sensorial contact model, 6 days after inoculation. Interactions carried out in the social stress were recorded in order to analyse their behaviour and to classify subjects in active or passive groups. Seventeen days after inoculation mice were subjected to sucrose preference test and on day 21, they were sacrificed and hippocampus was dissected in order to establish tryptophan (TRYP), serotonin (5-HT), 5-hydroxyindoleacetic acid (5-HIAA), kynurenine (KYN) and 3-HK levels.

Results indicate that tumor inoculated mice show lower 5-HT/TRYP ratio, lower KYN levels and a rise in the 3-HK/KYN ratio in the hippocampus. Tumor inoculated mice also show lower preference of sucrose than non-tumor mice. Stress do not result in tryptophan pathway changes but higher levels of 5-HIAA are observed in stressed mice in relation to non-stressed, independently of coping strategy. Furthermore, increased 5-HT levels are observed in active mice, but not in passive subjects when compared with non-stressed mice.

This data indicate that the neurotoxic pathway of the kynurenine may be activated by tumor which could contribute to the appearance of depressive-like behaviour. Furthermore, stress gives rise to changes that suggest an increase of serotoninergic hippocampal activity, regardless of tumor and coping strategy. However, the high levels of 5-HT observed only in active mice might suggest differences in neurotransmission depending on the strategy used when dealing with stress.

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Poster number: P-M050
Theme: The neurobiology of stress

Fear from height, anxiety, time of the day and diazepam in a 3D open-field

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When exposed to an unfamiliar open space environment, mice and rats experience fear and attempt to find an escape route. The presence of a challenging obstacle can prevent fear motivated escape in high anxiety mice. We exploited this fear motivated escape in a 3D open-field (OF) in order to assess anxiety in different mouse strains. The 3D OF consists of a platform with downward or upward inclined steep slopes (80cm x 25cm) attached on two opposite sides. In the downward slope configuration (DS), the platform is elevated 75cm (DS75) or 100cm (DS100) above ground. In the upward slope configuration (US), each slope leads to a stand (80cm x 25cm) and the platform is elevated 75 cm above ground (US75).

In DS75, DS100 and US75, mice spent more time in the areas adjacent to slopes than in the areas adjacent to void; only C57BL/6J and CD-1 crossed onto the slopes in DS75, and crossed onto the stands in US75. BALB/c explored the slopes in US75 only. The crossings onto the slopes in DS100 were significantly reduced in C57BL/6J and CD-1, and there were no differences between BALB/c and C57BL/6J. When tested in DS75 configuration, BALB/c mice demonstrated no difference in anxiety between early morning or late afternoon; they avoided the steep slopes and crossed onto shallow one. Administration of different doses of diazepam, but not amphetamine, facilitated crossings onto the steep slopes (DS75) in BALB/c mice.

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Poster number: P-M051
Theme: The neurobiology of stress

Investigating the link between epigenetic alterations and behavioral outcomes in a rodent model of early adversity

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It is widely recognized that the early postnatal environment, specifically within the context of the caregiving relationship, moderates the development of behavior and disease. Early, adverse experiences confer vulnerability to aberrant brain development, dysregulated immune function, anxiety and mood disorders, deficits in learning and memory, and a myriad of other consequences that persist throughout the life of the organism. Less understood are the mechanisms by which this disruption occurs, though epigenetic alterations have recently come to light as promising candidates. Our lab uses a model termed the scarcity-adversity model of low nesting resources wherein pup caregiver exposures occur outside the home cage with dams given very few nesting materials. This results in disrupted maternal care such that adverse behavior directed toward pups (i.e. dragging, dropping, stepping on, roughly handling, or actively avoiding pups) is significantly increased when compared to pups in the home cage, where nesting resources are plentiful. Using this model, our lab has previously reported altered methylation patterns of the brain-derived neurotrophic factor (bdnf) gene, a critical player in development and plasticity that is sensitive to stress and quality of caregiving. In the current experiment we have uncovered behavioral deficits in our adversity-exposed animals that parallel their altered epigenetic patterns. In order to investigate the link between these epigenetic and behavioral outcomes, we have administered epigenome-modifying drugs concurrent with caregiver manipulations. Preliminary data suggest that these agents can indeed prevent aberrant methylation patterns induced in adversity-exposed animals. Determining our ability to change (or prevent changes to) the epigenome is a critical first step in determining whether the relationship between those changes and later behavioral outcomes is a causal one.

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Poster number: P-M052
Theme: The neurobiology of stress

Expression of genes related with stress and behavioral regulation in dorsal hippocampus of the experimentally domesticated foxes

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The radical transformation of the animal behaviour toward human is a fundamental and major change occurred under domestication that accompanied by morphophysiological changes (e.g. appearance of floppy ears, curled tail, reduction of stress response). In the present work, we used a unique experimental model of the animal domestication, namely, “tame" silver foxes bred in Russia by long-term selection on emotionally positive reactions to humans. These foxes have the same behaviour, morphological and physiological changes as domesticated animals. The goal of this work is to identify differentially expressed genes and pathways for dorsal hippocampus between tame and aggressive foxes. For this, we used the RNA-Seq approach.

About half a thousand of differentially expressed genes were detected. The analysis of this data identified, among other, several pathways associated with the nervous system: “calcium signaling pathway” and “long-term potentiation” (e.g. genes of calcium voltage-gated channel subunit alpha1), “glutamatergic synapse” (e.g. NMDA-receptor genes), “GABAergic synapse” (e.g. the gene of a component of the GABA type A receptor). These genes and pathways are associated with the regulation of stress response,

neuronal plasticity and a number of forms of the behaviour, such as anxiety, fear, social recognition, learning and memory changed under historical domestication. In addition, the functional "axon guidance" group was allocated. The allocation of this group is probably associated with increased neurogenesis in adult hippocampus in less aggressive foxes as it was previously demonstrated.

Thus, changes in the expression of the genes of key neurohumoral brain systems that probably play a leading role in the change of the fox behavior during the selection on domestication was found.

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Poster number: P-M053
Theme: Neuronal, glial & cellular mechanisms

Formononetin Prevents Neuroinflammation-Mediated HT22 Neuronal Death

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Excessive activation of microglia during neuroinflammation is now known to exacerbate neuronal damage [1] in neurodegenerative conditions. Consequently, regulating the degree of microglia activation may be considered as an important strategy for treating neurodegenerative disorders. Formononetin (FMN) is a phytoestrogen present in food supplements like red clover. Earlier; we showed that FMN suppressed the release of pro-inflammatory cytokines in lipopolysaccharide (LPS)-activated BV2 microglia [2]. We also showed that the compound blocked neuroinflammation through mechanisms involving NF- κB signalling pathway [3]. In this study, we elucidated the neuroprotective effect of FMN in BV2 microglia/HT22 hippocampal neuron co-culture. BV2 microglia cells were pre-treated with FMN (2.5 10 µM) and then stimulated with LPS (1 µg/ml) for 24 h. HT22 cells were then exposed to BV2 microglia conditioned medium for 24 h. At the end of the experiment, neurotoxicity was determined using the MTT assay for cell viability. Levels of microtubule-associated protein-2 (MAP2) were detected by immunofluorescence and western blotting. MTT results showed that FMN significantly ($p<0.01$) prevented microglia conditioned media induced toxicity to HT22 neurons. Furthermore, western blotting reveals that pre-treatment with FMN produced a significant and concentration-dependent reversal of decreased neuronal MAP2 protein induced by microglia conditioned media. These results were confirmed with immunofluorescence imaging for MAP2. These results suggest that FMN prevents neuroinflammation-mediated HT22 neuronal death by inhibiting microglial activation.

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Poster number: P-M054
Theme: Neuronal, glial & cellular mechanisms

Cannabinoid regulation of excitatory synaptic transmission at hippocampal TA-CA1 synapses

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The endogenous cannabinoid system, composed of neuromodulatory endogenous lipid ligands and their cannabinoid receptors, has crucial physiological and regulatory roles throughout the body. It is known that cannabinoids produce their biological effects via activation of CB1 and CB2 receptor subtypes (Battista et al., 2012), however in the CNS, the predominant cannabinoid receptor is CB1. Numerous studies have examined the modulatory effects of cannabinoids on excitatory synaptic transmission at hippocampal schaffer collateral (SC)-CA1 synapses. Indeed, evidence suggests that hippocampal cannabinoid receptors not only play a role in learning and memory formation, but they are also linked to neurodegeneration in Alzheimer's disease (AD) (Hajos and Freund 2002). However the effects of cannabinoids on excitatory synaptic function at the anatomically-distinct temporoammonic (TA) input to CA1 neurons is not clear. Here, standard extracellular recordings were used to examine the effects of different selective agonists for CB1 receptors on excitatory synaptic transmission at the juvenile TA-CA1 synapses. Transverse hippocampal slices (350µM) were prepared from 12-18 rats and perfused with oxygenated aCSF. Application of (R) - (+) - methandamide (50nM; 15min) resulted in a transient increase (to 137 ± 7.1% of baseline; n=4; $p<0.001$) in excitatory synaptic transmission that returned to baseline on washout (104 ± 0.7% of baseline; n=4; $p>0.05$). On the other hand, application of ACEA (10nM; 15min) had no effect on synaptic transmission at TA-CA1 synapses (102 ± 0.7% of baseline; n=4; $p>0.05$). These data indicate that CB1 receptor activation modulates excitatory synaptic transmission at hippocampal TA-CA1 synapses. These findings may be important as the TA pathway plays a role in episodic memory (Remondes & Schuman 2004) and impairments in episodic memory is an early event in AD (Hodges 2000)

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Poster number: P-M055
Theme: Neuronal, glial & cellular mechanisms

The effect of chronic amphetamine treatment on the morphological characteristics of the superficial superior colliculus in the rat

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Heightened distractibility refers to a reduced ability to discriminate relevant from irrelevant information. It is found in normal ageing and a number of psychiatric conditions, including attention deficit hyperactivity disorder (ADHD), dyslexia, schizophrenia, and depression. The most effective form of treatment for heightened distractibility are psychostimulant drugs, such as amphetamine. These are administered orally and often prescribed over prolonged periods, despite unclear mechanisms of action. Converging evidence suggests that a potential neural correlate for distractibility is the superior colliculus (SC). Alterations to this structure and its connections to the prefrontal cortex have been found to increase distractibility and collicular abnormalities are implicated in ADHD. Furthermore, we have recently shown changes in collicular-dependent behaviour and visual responsiveness in this region after amphetamine treatment, indicating that the therapeutic mechanism of action to reduce heightened distractibility may be, at least in part, within the SC. To date, however, there has been no systematic characterisation of the morphological features of the SC following chronic administration of amphetamine, despite such features being altered in other brain areas following similar treatment.

We chronically treated male Hooded Lister rats for a four week period with orally administered amphetamine (2 mg/kg, 5 mg/kg and 10 mg/kg) and compared the brains of these animals to untreated control animals and animals treated with a vehicle solution (distilled water). Following treatment, animals were perfused and the brains fixed. Brains were sectioned into 50 µm slices and Nissl stained for measures of collicular volume (employing the Cavalieri principle), neuron and glial cell counts and densities. Additional sections were used for immunohistochemistry to detect synaptophysin. Finally, we perfused a subset of animals separately to conduct a Golgi stain on 100 µm slices through the colliculus in order to examine the microstructure of the region. Specifically, we measured dendritic branching, spine density and spine type in the region. Volumes, cell counts and densities were unaffected, although sub-cellular changes were apparent.

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Poster number: P-M056
Theme: Neuronal, glial & cellular mechanisms

Effect of sub-chronic phencyclidine treatment on dopamine receptor gene expression in the rat brain

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Schizophrenia is a debilitating mental disorder affecting ~0.5% of the population, yet the neurochemical basis is poorly understood. Phencyclidine (PCP), an antagonist at NMDA-type glutamate receptors causes psychotic symptoms in normal people, and exacerbates symptoms in schizophrenia sufferers. Thus, short-term chronic pre-treatment with PCP (termed sub-chronic) in experimental animals has been proposed as a model for schizophrenia. Despite this central role of glutamate, dopaminergic signalling is also known to be involved in symptom expression, and PCP may have downstream effects on dopamine systems, particularly in the mesolimbic pathway, perhaps mediated through changes in dopamine receptor expression.

However, the changes in expression of dopamine receptors in dopaminergic brain regions following sub-chronic PCP pre-treatment are unclear. In this study, we investigated the expression of dopamine receptor mRNA in nucleus accumbens, (NAc), frontal cortex (FCx) and ventral tegmental area (VTA), brain regions associated with the mesolimbic dopamine pathway, in rats, 21 days after sub-chronic pretreated with PCP for 5 days.

Female Lister-hooded rats (c250g at start) were pretreated sub-chronically with PCP (2mg/kg, I.P) or saline (1ml/kg, I.P) twice/day for 5 days. They then remained drug-free for 21 days before being humanely killed, the brains removed and the areas of interest dissected out. Expression of the dopamine receptors (D1, D2, D3, D4, and D5) was measured by real-time quantitative polymerase chain reaction (RT-qPCR).

Looking at the terminal fields of the mesolimbic pathway, in NAc, we found increased expression of D1, D2 and D3, while in FCx we found increased expression of D2 and D3 receptors, and decreased expression of D4 receptors. In the cell body region in VTA, we found a decrease in D2 and D5 receptor expression.

In conclusion, there were differences in expression of dopamine receptors between saline pre-treated and PCP pre-treated in both cell body and terminal regions of the mesolimbic pathway. These changes may underlie some of the behavioural deficits seen after PCP pretreatment, and may be important in our understanding of the mechanisms underlying schizophrenia.

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Poster number: P-M057
Theme: Neuronal, glial & cellular mechanisms

The proton-sensing receptor OGR1 modulates intracellular calcium homeostasis in HEK293 cells

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OGR1 is a proton-sensitive GPCR widely expressed throughout the mammalian body, including neurons[1, 2]. OGR1 is thought to play a role in pH homeostasis [3], and has been implicated in reducing tumour metastasis[4]. We transiently transfected HEK293 cells with a HA-tagged OGR1 construct to evaluate effects of receptor activation on intracellular calcium homeostasis (calcium levels measured using Fura-2-based microfluorimetry). Treatment of OGR1-transfected cells with acidic buffer (pH 6.8) for 15 min led to an increase in calcium levels. These calcium responses were variable, with single spike or oscillatory responses detected. Responses were reproducible on repeated challenge with acidic buffer, supporting previous claims that OGR1 does not desensitise[2, 3]. No effect of acidic buffer on calcium levels was observed in untransfected, control cells. However, these cells showed marked responses to carbachol. Treatment with the Gq inhibitor, YM-254890 (0.5 µM, 20 min) abolished all calcium responses in proton-sensitive HEK HA-OGR1 cells and responses to carbachol in controls. As OGR1 signals through Gq[3] this effect supports a role for HA-OGR1 in mediating calcium responses to acidic buffer treatment. Much of the published work on OGR1 has focused on cAMP and IP3 formation [3, 5]. This study provides insight into the effects of OGR1 activation on intracellular calcium levels and the effects of acidic buffer treatment on OGR1 mediated downstream signalling. Next we aim to explore the effects of native OGR1 activation on neuronal intracellular calcium homeostasis.

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Poster number: P-M058
Theme: Neuronal, glial & cellular mechanisms

Deriving microglia from human induced pluripotent stem cells

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Immune activation within the CNS is a classical feature of neurodegenerative diseases. It is now increasingly evident that diseases such as Alzheimer's and Huntington's trigger local inflammation and activate innate immune responses, which are primarily driven by microglia. Though recent years have seen a growing appreciation of the importance of research into the role of microglia-mediated inflammation, there is currently an unmet need for human in-vitro microglial models that enable in-depth mechanistic studies and bridge the gap between clinical and animal models. We have developed a protocol that enables differentiation of microglia-like cells from human iPS cells. Firstly, stem cells were differentiated to monocytes expressing the myeloid-specific marker CD14 as well as the haematopoietic markers CD45 and CD11b. Monocytes were further directed to a ramified microglial phenotype by treatment with the growth factors GM-CSF and IL-34 and by interaction with astrocytes and neurons. The iPSC-derived microglia were discriminated from macrophages and other monocyte lineage cells by the defining marker expression profile TMEM119+/IBA1+/GLUT5+/CD45low/CSF1Rhigh/TREM2high. The iPSC-derived microglia have been functionally validated against anticipated phenotypes including cytokine production, phagocytosis and intracellular signalling, and comparisons made with unstimulated cultures. Moreover, gene expression profiling has identified genes and pathways involved in the regulation of microglial response to amyloid beta. The development of protocols for the generation of in-vitro microglial models holds great significance in Alzheimer's disease research as it will allow to investigate the contribution to the disease process of microglia and microglia-enriched genes identified as risk factors for Alzheimer's disease.

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Poster number: P-M059
Theme: Neuronal, glial & cellular mechanisms

Characterising dopaminergic plasticity in the mouse olfactory bulb

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Olfactory bulb dopaminergic neurons are inhibitory interneurons that co-release dopamine and GABA to regulate the early processing of odour information in the glomerular layer. These neurons can be readily identified by the expression of tyrosine hydroxylase (TH), the rate-limiting enzyme of catecholamine synthesis. We use a Cre-driver mouse line under the control of the dopamine transporter (DAT) crossed with a tdTomato reporter mouse to label dopaminergic neurons allowing for visual targeting in live preparations. Initial experiments have been to characterise the coverage and specificity of the labelling in these transgenic mice. Most DAT-tdTomato neurons were positive for TH (approximately 75%). TH expression is known to be activity-dependent in the olfactory bulb, therefore, the TH-negative neurons could still be dopaminergic. Staining with another dopaminergic marker, dopa decarboxylase (DDC), reveals co-localisation with TH-positive neurons and absence from DAT-tdTomato neurons that are TH-negative. Investigating markers of other known glomerular layer neurons demonstrated that this subpopulation is part of the calretinin population of neurons.

Olfactory dopaminergic neurons are known to be particularly plastic, altering their structure, function and gene expression in an activity-dependent manner. We use slice electrophysiology and immunohistochemistry to examine experience-dependent changes in DAT-tdTomato neurons after one and three days of unilateral naris occlusion. Using this data, we will investigate how functional plasticity is regulated by activity-dependent changes in gene expression and epigenetic modifications in these neurons.

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Poster number: P-M060
Theme: Neuronal, glial & cellular mechanisms

STP and LTP in the GluN2D knockout mouse

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NMDA receptors (NMDARs) are critically involved in the induction of short-tern potentiation (STP), long-term potentiation (LTP) and long term-depression (LTD) in the CA1 area of rat hippocampus. In this regard, we have shown that different di- and tri-heteromeric NMDARs are involved in the induction of the three forms of synaptic plasticity (Volianskis et al 2013, 2015; France et al 2016). Thus, GluN2D containing NMDARs were found to be involved in STP but not in LTP or LTD. Induction of LTP was mediated by tri-heteromeric GluN2A/2B containing NMDARs whereas GluN2B containing di-heteromers were found to be involved in LTD.

Here we studied for the first time the functional implications that knocking out the GluN2D subunit exerts on the induction of STP and LTP. We found that both STP and LTP can be readily induced in hippocampal slices from the GluN2D knockout mice (KO). Notably, whilst GluN2D preferring antagonist UBP145 had no effect on the induction of STP and LTP in the GluN2D KO, it partially blocked LTP in slices from the wild-type littermate controls. These data confirm the specificity of UBP145 and highlight the involvement of GluN2D subunits in the induction of LTP in mouse, in stark contrast to the rat. Moreover, both STP and LTP were partially inhibited by either 0.1 µM NVP-AAM077 or 10 µM Ro 25-6981 in the GluN2D KO and a combination of both antagonists completely blocked the induction of potentiation. This suggests that GluN2A/2A di-heteromers and GluN2A/2B tri-heteromers mediate the induction of STP and LTP in the GluN2D KO.

In summary, our results indicate that the pharmacological profile for inhibition of STP and LTP is altered in the GluN2D KO, suggesting a complex combination of compensatory effects. Furthermore, and in contrast to the rat, GluN2D-containing NMDARs appear to be important in the induction of LTP in mouse, suggesting species differences in the role of NMDAR subunits mediating the induction of synaptic plasticity.

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Poster number: P-M061
Theme: Neuronal, glial & cellular mechanisms

Glial Activation Following Nerve Graft Repair and Local Administration of Mannose-6-phosphate

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Introduction: Mannose-6-phosphate (M6P), a potential scar reducing agent, has previously been shown to enhance nerve regeneration, but its effects on the development of neuropathic pain following nerve injury remain unknown. Spinal glial activation has been reported as a key regulator of neuropathic pain and differences in activation levels may reveal further benefits of M6P treatment. There are many potential ways to treat the site of nerve repair with M6P; its addition to fibrin glue used in the repair could provide a simple method of therapeutic dosing.

Aims: The aim of the study was to investigate whether the application of M6P in fibrin glue results in differences in spinal glial activation following peripheral nerve repair.

Methods: 10 thy-1-YFP-H mice and 10 wild type mice were used. The common fibular nerve of thy-1-YFP-H mice was transected and a 3 mm gap was made. A nerve graft of 3 mm was obtained from wild type mouse and placed within the gap. The nerve ends and graft were then aligned and secured by fibrin glue with/without M6P (600mM). After 2 weeks, spinal cords were harvested, fixed and prepared for immunohistochemistry to label microglia and astrocytes.

Results: Glial activation was increased on the injured side for both repair groups. While no significant differences were observed between repair groups, activation was generally higher in the ventral horn for the non-M6P group, with astrocyte activation at 134.9% and microglia activation at 127.2% of the uninjured side values compared to 128.7% and 123% respectively in the M6P group. Differences in the dorsal horn were mixed, with astrocyte activation lower at 125.9% and microglia activation higher at 136.8% of the uninjured side values in the M6P group, compared to 128.5% and 129% respectively in the non-M6P group.

Conclusion: No significant differences in glial activation were observed between the use of fibrin glue implanted with M6P and fibrin glue alone. However, the differences observed in microglia activation (higher in dorsal horn, lower in ventral horn) appear to suggest that M6P may be more beneficial towards motor axons than sensory. Further investigation may be warranted in order to confirm the validity of this effect and, if confirmed, elucidate a potential mechanism of action.

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Poster number: P-M062
Theme: Neuronal, glial & cellular mechanisms

GABAergic modulation of dopamine release in nucleus accumbens, measured by fast scan cyclic voltammetry in rat brain slices in vitro

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The dopamine (DA) theory of schizophrenia posits a key role for DA dysfunction: drugs used in treatment share a DA antagonist action. However, glutamate systems are also critical: phencyclidine (PCP: NMDA glutamate receptor antagonist) causes psychotic symptoms in normal people and exacerbates symptoms in schizophrenia sufferers. In rats, short term chronic PCP treatment causes behavioural deficits mimicking schizophrenia symptoms, which endure long after the end of drug treatment, providing an animal model for studying processes underlying the disease.

Core deficits in glutamate function may impinge on DA systems, particularly in nucleus accumbens (NAc). Release of DA in NAc is under modulatory control of many transmitter systems, including GABA, and abnormalities in this modulation may underlie changes seen after PCP pretreatment. This study aimed to characterise GABA mechanisms modulating DA release in NAc, and to ascertain whether these were changed after PCP pretreatment, giving potential insights into mechanisms involved in schizophrenia.

Coronal slices (400µm) containing NAc were cut from juvenile female Wistar rat (c24 days) brains and placed in a 1ml tissue chamber, superfused continuously with oxygenated artificial cerebrospinal fluid (aCSF: 2 ml/min; 33°C). Fast cyclic voltammetry (FCV) scans (-0.4V to +1.3V to -0.4V; 400V/sec) were applied at 10Hz and DA was measured as the background subtracted current occurring at 600mV.

Twelve trains of electrical stimulations (30 pulses; 60Hz; 300uA) were applied at 3 min intervals and evoked DA release was measured. After 4 stimulus trains, drugs were applied in the superfusate for 12 min (i.e. until after stimulus 8), and a further 4 stimulations were applied during washout. Control slices underwent the same 12 stimulus trains, but were superfused with aCSF throughout.

Both muscimol (GABA-A agonist) and baclofen (GABA-B agonist) caused dose dependent attenuation of electrically stimulated DA release at 1, 10 and 100 µM. Therefore GABA systems exert inhibitory control over DA release in NAc, via both GABA-A and GABA-B receptors, which may be abnormal after PCP pretreatment.

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Poster number: P-M063
Theme: Neuronal, glial & cellular mechanisms

Modification of microglial apoptosis alters their functional response to an inflammatory stimulus

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Microglia, the brain's resident immune cells, have many functions including the regulation of inflammation in brain disease and monitoring synaptic activity. In the healthy murine brain, microglial cell density remains constant throughout life, maintained by a fine balance of proliferation and apoptosis1. It remains unclear how altering microglial population dynamics may affect microglial function and brain physiology. In order to study this, we utilised the Vav-Bcl2 transgenic mouse2 which has a block of intrinsic apoptosis in cells of the myeloid lineage, including microglia, due to overexpression of human Bcl2 under the Vav promoter. Vav-Bcl2 mice have significantly increased microglial cell density throughout the brain, which peaks at postnatal day (P)44 and is maintained throughout adulthood, with no gross differences in neuronal or astrocyte populations. In particular, elevated numbers of the CD11b+CD45hi subset of microglia contribute to the increase in cell density, suggestive of an altered functional state in the brain compared to wild-type controls. Transcriptomic analysis of isolated microglia revealed differential expression of genes involved in metabolic processes, macromolecule biosynthesis and immune response, indicating that deregulation of microglial apoptosis changes their phenotype. This altered phenotype is associated with an exacerbated pro-inflammatory response in the brains of Vav-Bcl2 mice after systemic challenge with LPS. Our data shows that long-term deregulation of apoptosis in microglia results in significant phenotypic changes and alters their functional response to an inflammatory stimulus. Deregulation of microglia population dynamics throughout the life-course may have implications for the onset and progression of age-related neurological diseases.

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Poster number: P-M064
Theme: Neuronal, glial & cellular mechanisms

Using human iPSC-derived neural progenitor cells to increase integrin expression in the CNS

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Regeneration of the adult CNS is an ongoing challenge with many obstacles. Repair of mature neurons is limited largely down to two factors: the growth-inhibiting environment created after injury and the innate inability of CNS neurons to repair. In contrast to mature, aged neurons, during embryonic cortical development, neurons have a high capacity for plasticity, regeneration and repair. This may be due to the fact these cells express growth-promoting proteins called integrins. Integrins are transmembrane receptors involved in mediating cell-cell and cell-matrix interactions. Within the adult CNS, integrin expression is downregulated resulting in reduced plasticity and growth. Literature indicates increasing integrin expression in adult CNS axons can promote regeneration; however recent research suggests exogenous integrin expression in vivo results in the inability of integrins to travel down adult CNS axons which instead remain localised to the cell body.

In light of this, here stem cells are used as a vehicle to increase integrin expression within the CNS. With a regenerative approach in mind, we have grafted iPSC-derived NPCs into cerebral cortex of rodents. Using a combination of western blotting and immunofluorescence techniques, we determined both the endogenous expression level of integrin within iPSC-derived NPCs and the expression level following viral-mediated transduction. To assess transplant survival, neonatal cortical grafting of hNPCs was carried out. Using specific coordinates, wild type and integrin-expressing hNPCs were injected into layer V of the sensorimotor cortex of P0-aged rats. Following grafting, animals were perfused at 2, 4, 6, 7 and 8 weeks of age. In Sprague Dawley rats, wild type hNPCs are able to put out axonal projections up to 8 weeks in vivo. Further IHC analysis shows, grafted cells express deep-layer cortical neuron markers, and, as expected, are inducing a host immune response. Analysis of neurite length in vitro indicates the

exogenous integrin is functional, promoting significant neurite outgrowth compared to controls. In analysis of integrin-expressing hNPC transplants we have shown the grafted hNPCs retain their exogenous integrin expression within the axonal compartment up to 8 weeks in vivo.

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Poster number: P-M065
Theme: Neuronal, glial & cellular mechanisms

Investigating expression of Notch signalling pathway in cells of the neurovascular unit

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Background
Notch receptors and their ligands form a fundamental intra-cellular signalling pathway that controls maturation, proliferation and apoptotic events during development.[1] Mutations in the NOTCH3 gene cause the early-onset stroke disorder cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).[2] CADASIL is characterised by pathological changes within arteries and arterioles, resulting in disability and early-onset dementia.[3] Genetic variation in NOTCH3 has also been associated with increased risk of vascular changes in older people.[4, 5] Cerebral blood vessels are maintained by cells within the neurovascular unit (NVU).[6] It is not known whether CADASIL-causing NOTCH3 mutations interrupt Notch signalling, or how hypoxia influences the Notch pathway components within the NVU. We aimed to characterise the expression of the Notch pathway in the cell types of the NVU before and after hypoxia.

Methods
Rat C6 glioma and human umbilical vein endothelial cells (HUVECs) were cultured under normal cell culture conditions until 75% confluence, at which time cells were exposed to hypoxia (2% O2) for 45 minutes, 2, 4, 12, 24 and 48 hours. Total RNA was extracted using phenol/chloroform phase separation before cDNA synthesis for quantitative PCR assessment of changes in expression of NOTCH and hypoxia signalling pathways.

Results
Expression profiles of the NOTCH pathway components were defined for both cell types under normoxia and following hypoxia of increasing time periods.

Conclusions
Herein we report a full assessment of the expression pathway of NOTCH pathway components in cellular models of components of the NVU and the effects of hypoxia on their expression. The findings from these experiments will allow us to further develop cellular models of the NVU which can be utilised in the identification of novel drugs for the treatment of stroke and CADASIL.

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Poster number: P-M066
Theme: Neuronal, glial & cellular mechanisms

Short-term plasticity of striatal dopamine release is governed by release-independent depression and the dopamine transporter

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Dynamic changes in the rate and pattern of action potential generation in midbrain dopaminergic neurons are thought to encode behaviourally-relevant information about salient and/or rewarding stimuli. These neurons project extensively branched axons to the striatum, where the release of dopamine (DA) does not necessarily represent a faithful read-out of presynaptic firing activity. DA signalling will be shaped by presynaptic mechanisms that determine the probability of DA release (Pr) and its short-term plasticity (STP), but these mechanisms are poorly understood. We measured evoked DA release using fast-scan cyclic voltammetry in slices of mouse striatum to explore key candidate mechanisms. We show that STP of DA release is characterised by facilitation at short inter-pulse intervals, and depression at longer intervals, as previously described. Large changes to release probability driven by changes to extracellular Ca2+ had only weak effect on STP, suggesting a limited dependence of STP on release probability. Instead, STP was primarily governed by release-independent mechanisms; changes in extracellular K+ likely to modify membrane potential and repolarisation did not change initial release probability but strongly modified STP. Since the dopamine uptake transporter (DAT) can influence dopamine release and membrane potential of DAergic neurons, we also investigated a potential role in STP. Pharmacological inhibition of the DAT reduced both facilitation and depression, and precluded modulation of STP by changes in extracellular K+. These findings reveal the DAT has dual roles on dopamine release, both limiting initial release probability and permitting STF at highest frequencies, and promoting release-independent depression through an interaction with K+-dependent processes. These mechanisms may give rise to the preferential reporting of high-frequency presynaptic activity by DA release, in conditions where the DAT is active.

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Poster number: P-M067
Theme: Neuronal, glial & cellular mechanisms

Mapping Synapses and Astrocytic Processes in the Mammalian Spinal Cord

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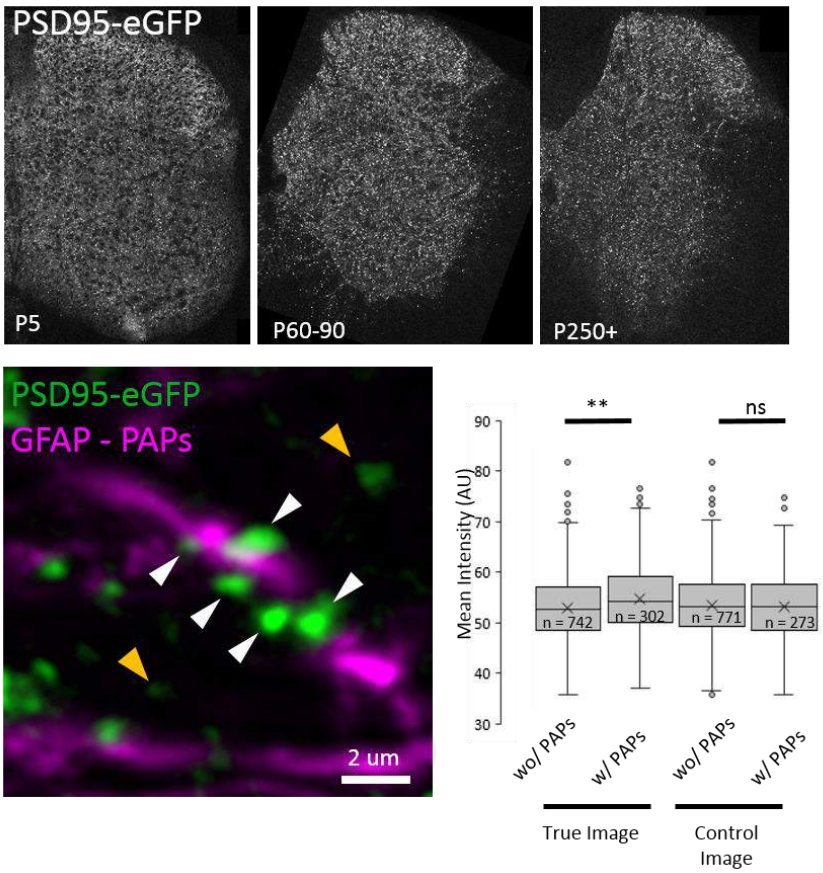
The spinal cord contains the neural circuitry necessary for the generation of movements such as locomotion, as well as sensation and pain detection. Anatomically different neural circuits may show structurally and molecularly distinct synaptic features and that could also vary over development and ageing. In addition, astrocytes in the central nervous system, which associate with synapses via perisynaptic astrocyte processes (PAPs), may contribute to this synaptic diversity. Large scale mapping of both synapses and astrocytes together could therefore provide a more detailed understanding of the factors affecting synaptic physiology within distinct neural circuits.

In this study, we have used a genetically engineered mouse expressing fluorescently labelled PSD-95 and quantitative microscopy methods to map excitatory synapses and PAPs in the spinal cord. From large scale image analysis of synapses, we show inter-regional and age dependent diversity in excitatory synapse structure and molecular composition. We further used super-resolution microscopy to interrogate the structural differences between synapses of different spinal cord circuits, namely dorsal and ventral horn synapses.

Combining synapse analysis with immunohistochemistry staining of astrocytes, we show the degree of synapse association with astrocytes varies between ages. Furthermore, synapses found with a PAP are found to be structurally larger and molecularly more enriched with PSD-95 than synapses without a PAP. Furthermore, we find that the nature of this interaction between astrocytes and synapses was different between sub-regions of the spinal cord, and between different age groups.
Our data provides a thorough baseline understanding of excitatory synapse diversity in the spinal cord, providing insights into the functional differences between sensory, integrational, and motor circuits. Furthermore, we have applied a highly quantitative microscopy approach to study the relationship between synapses and astrocytes. We show that synapses are structurally and molecular enriched when contacted by astrocytes, and the nature of this interaction changes between ages and between different neural circuitry.



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Poster number: P-M068
Theme: Neuronal, glial & cellular mechanisms

Preferential activation of HIF-2 adaptive mechanisms in neuronal-like cells in response to hypoxia

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Stroke is a leading cause of death and disability worldwide. Blockage, or occlusion, of cerebral arteries causes irreversible neuronal damage as disrupted blood flow starves neurones of oxygen and glucose. The hypoxia inducible factors (HIFs) are master regulators of oxygen homeostasis and critical for adaptation to hypoxic insult. Although HIF-1 and HIF-2 share some common gene targets, they also promote specific adaptations to hypoxia. Differentiated PC12 and NT2 cells have been extensively used as a model to study the molecular changes associated with neurological pathologies, such as stroke. In this study, differentiated PC12 and NT2 cells were exposed to hypoxia for 4-24 hours in a hypoxic modular chamber before gene and protein expression was analysed by qPCR and immunoblotting. In order to validate the model, we characterised the in vitro changes associated with differentiation into neuronal-like cells, observing morphological, transcript and protein changes that revealed a neuronal-like phenotype. Following hypoxia, induction of the HIF-1 transcript or protein expression was not detected. Curiously, preferential activation of HIF-2 transcription and protein expression was detected. Increased expression of the neural progenitor stem cell-like markers, thought to be transcriptionally regulated by HIF-2, were also observed. Furthermore, hypoxia caused loss of neuronal characteristics in the differentiated cells, as seen by a decrease in the expression of the neuronal markers, and loss of neurite number and extension. Our data shows the HIF-2 pathway predominates over the HIF-1 pathway in neuronal-like cell adaptation to hypoxia, and suggests such adaption could promote regression to neural progenitor stem-cells and thus, potentially proliferative states. This is highly significant as it shows neuronal cells possess molecular mechanisms which could trigger recovery following ischaemic insult. By completely understanding such adaptive mechanism and translating these results to in vivo models, it could represent a novel therapeutic approach to stimulate recovery after stroke.

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Poster number: P-M069
Theme: Neuronal, glial & cellular mechanisms

Hippocampal Innervation of Parvalbumin Interneurons in Prefrontal Cortex

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Prefrontal cortex (PFC) receives a direct glutamatergic projection from the hippocampal formation (HPC) and this connection is important in working and recognition memory. The pathway terminates on both excitatory pyramidal neurons and inhibitory interneurons within the PFC (1). Little is known about how HPC modulates the activity of interneurons in the PFC.

Using a transgenic mouse line to target parvalbumin (PV) interneurons (PVCre/tdTomato) and in vitro slice electrophysiology techniques we examined the role of NMDA and AMPA receptors (NMDAR, AMPAR) in controlling synaptic transmission between HPC and PV interneurons within the prelimbic PFC.

Whole-cell voltage clamp recordings were obtained while electrically stimulating the hippocampal fibre tract. The current-voltage (I-V) relationship was examined for both AMPAR and NMDAR mediated currents. The AMPAR I-V curve was inwardly rectifying, indicating the presence of GluR2-lacking AMPARs. The NMDA I-V curve showed a typical relationship for these channels, with the initial negative slope and the maximum peak amplitudes occurring at depolarised holding potentials. We examined the relative contribution to synaptic transmission of AMPAR and NMDAR-mediated currents and found a low NMDA/AMPA ratio (0.25±0.03, n=10). This indicates that synaptic transmission is largely mediated by GluR2-lacking AMPA receptors. We have recently shown that NMDARs contribute to HPC-PFC pyramidal cell transmission in a frequency dependent manner (2). Our preliminary data suggests that NMDARs play a role in summation at HPC-PV interneuron synapses during high frequency transmission (50 and 100 Hz). To compliment electrophysiological recordings, we built a neuronal model in Python to simulate the glutamatergic synapse onto the interneurons. We optimised the parameters for AMPA and NMDA receptor-mediated currents using a Nelder-Mead method and we are currently using the model to investigate synaptic summation at the HPC-PV synapse.

Determining the role of PV interneurons in controlling HPC-PFC circuit functions will be important in understanding the role of these neurons in working and recognition memory.

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Poster number: P-M070
Theme: Neuronal, glial & cellular mechanisms

Bidirectional interaction between endocanabinoid and retinoid signalling pathways in the brain

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Lipids play a central role in the function of the brain as structural components. An important additional role of lipids though is to act as signalling molecules to control function, both during development and within the mature brain. Two major lipid-signalling routes are the endocannabinoid (1) and retinoic acid signalling systems (2) acting respectively through the cannabinoid CB1 or CB2 G-protein coupled receptors or the RARα, β or γ ligand gated transcription factors. Both have essential roles to control neuroplasticity and cross-talk between the two pathways may have a profound effect on the brain. We have looked for interactions between the retinoid and endocannabinoid signalling pathways by determining the ability of a CB1/CB2 receptor agonist to target retinoid genes and of a RAR agonist to target genes involved in endocannabinoid signalling. The pathways were studied in the stem-cell-like embryonal carcinoma (P19) cell-line and rodent primary cultured neurons. Retinoic acid was found to regulate CB1 receptor gene (Cnr1) expression as well as the metabolic enzyme diacylglycerol lipase (DAGLα). Conversely, the cannabinoid CB1 and CB2 agonist (CP55, 940) was found to influence the retinoid signalling system by altering expression of the receptor genes Rara and Rarb, as well as expression of the gene encoding the metabolic enzyme Raldh1. This work demonstrates that the endocannabinoid signalling system and retinoid system may have primary or secondary influences on one another in the central nervous system.

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Poster number: P-M071
Theme: Neuronal, glial & cellular mechanisms

Characterising the role of amphoterin induced gene and open reading frame 3 (AMIGO3) in the pathogenesis of, and treatment for demyelinating diseases

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Demyelination disrupts neuronal signalling leading to impairment in neurological control. In multiple sclerosis (MS) as well as other demyelinating diseases, oligodendrocyte precursor cells (OPC), which are present in large numbers in the central nervous system, survive but do not mature and produce myelin. Leucine rich repeat (LRR) molecules such as LINGO1 have recently been shown to play a role in inhibiting the maturation and myelin production of OPC. We have identified a novel LRR Amphoterin Induced and Open Reading Frame 3 (AMIGO3), with similar properties and interacting partners as LINGO1, which appears to be important within the murine central nervous system. As such, AMIGO3 is predicted to be a novel inhibitor of OPC maturation. We observed the expression profile of AMIGO3 in the cerebral cortex and corpus callosum during postnatal development in BALB/c mice through semi-quantitative immunohistochemistry and western blot analysis. AMIGO3 protein expression is greatly upregulated at postnatal day 7 (P7) in the cerebral cortex, followed by a steady decline to P28. This demonstrated an inverse correlation with the extent of myelination. Interestingly there is no obvious correlation between signs of OPC maturation and AMIGO3 expression suggesting that AMIGO3 does not affect maturation but purely the production of myelin. We further analysed the expression of AMIGO3 in in vitro and in vivo models of trauma. This was in line with previous observations of raised AMIGO3 protein expression in the acute and chronic stages following spinal cord trauma. AMIGO3 was observed to increase between 1.5-2x ($P<0.05$) following excitotoxic treatment with AMPA-CTZ in Oli-neu cells. AMIGO3 was also observed in early stages of experimental autoimmune encephalomyelitis (EAE). These data suggest that AMIGO3 is playing a role within oligodendrocytes following trauma and thus is likely to be a promising therapeutic target. We further intend to examine AMIGO3 protein expression, as well as common signs of inflammation and demyelination, in later stages of acute EAE and human MS to gain an insight into the roles of the protein during the progression of demyelinating diseases.

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Poster number: P-M072
Theme: Neuronal, glial & cellular mechanisms

Impaired astrocytic IP3R2 signalling interferes with experience-dependent plasticity (EDP) in layers 2/3 of the murine barrel cortex

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In response to changes in whisker experience of adolescent mice, cortical neurons in layers 2/3 of the murine barrel cortex can exhibit two general forms of experience-dependent plasticity (EDP): coding plasticity (CP) and homeostatic plasticity (HP). CP refers to changes in neuronal transmission and connectivity of individual synapses and is thought to enable information storage within a neuronal network. HP is most often a global phenomenon that acts as a negative feedback mechanism to keep the activity of a neuronal network within a set operating range. To determine possible astrocyte roles in both CP and HP we utilised IP3-R2 knock out (KO) mice, in which astrocytes but not neurones exhibit diminished [Ca2+] responses. To evoke CP, all but one whisker (single-whisker experience – SWE) were removed unilaterally for 18 days, followed by regrowth for 5-9 days. To evoke HP, all whiskers were trimmed unilaterally for 1, 3, 7, 14, 25 and 32 days and re-attached on the day of recording. We found no significant differences in the magnitude of principal and surround responses in undeprived WT and KO mice and in the amount of plasticity

induced in SWE animals (all pairs p>0.05, U-test, N=20). In all-whisker-deprived WT animals the principal whisker responses showed rapid depression 1 day after deprivation (t-ratio 7.3, p<0.0001, N=15), started to recover at 3 days, were above control levels at 7-14 days (t-ratio 3.7, p<0.003, N=15), indicating HP, and back to control levels at 25-32 days. However, IP3-R2 KO mice exhibited a linear decay in magnitude of responses with deprivation time which was significant after 14 days (p<0.05, N=6) with an impaired HP rebound at 25 and 32 days which was not significant (p>0.05, N=10). In both acute slice experiments and in vivo , the LTD induction protocol induced LTP in the KO mice. This scenario was also mimicked in WT slice recordings by patch electrode filling of astrocytes with the calcium chelator BAPTA. LTP induction protocol induced LTP in KO slices, but not in WT slices after filling of astrocytes with BAPTA. This data implicate astrocytes as potent regulators of experience-dependent coding depression and homeostatic up-regulation of whisker-evoked responses.

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Poster number: P-M073
Theme: Neuronal, glial & cellular mechanisms

Succinate supplementation improves metabolic performance of mixed glial cell cultures with mitochondrial dysfunction

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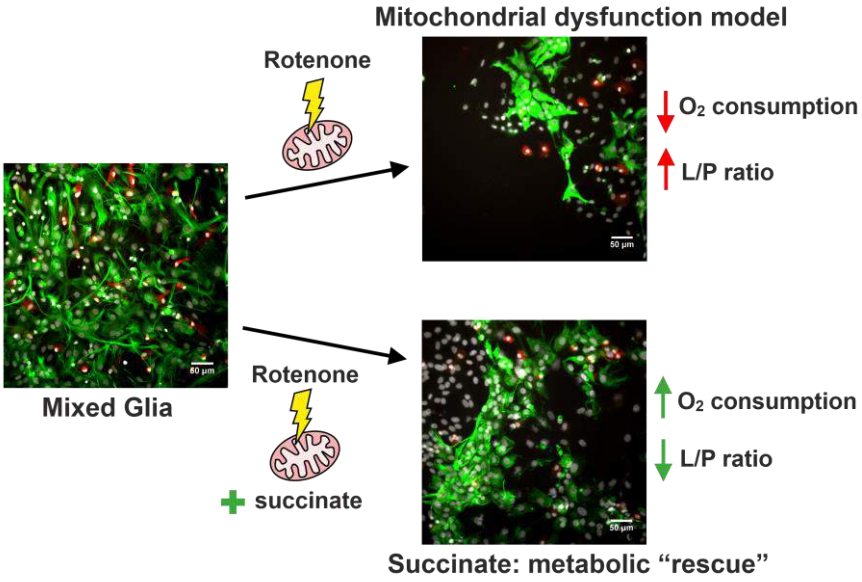
Following traumatic brain injury (TBI) or spinal cord injury (SCI), complex pathological processes evolve in which cerebral energy perturbations play a major role. In some circumstances mitochondrial dysfunction, where the brain is unable to utilise metabolic fuels and oxygen despite adequate provision, is thought to be responsible for these energy perturbations. Succinate is a tricarboxylic acid (TCA) cycle intermediate which interacts directly with the mitochondrial electron transport chain (ETC). The results of a recent study by our research group suggest that focal administration of succinate, via a microdialysis catheter inside the brain, could improve brain metabolism in TBI patients by fuelling and enhancing the TCA cycle even in the context of mitochondrial dysfunction. The aim of this study was to determine whether succinate supplementation can improve cellular energy state under induced conditions of metabolic stress in a tissue culture model, to confirm and provide better understanding of the results obtained in succinate-treated patients. An overview of the findings of this study is shown in Fig 1. Primary mixed glial cell cultures comprising astrocytes, oligodendrocytes and microglia, were exposed to rotenone (an inhibitor of Complex I of the mitochondrial ETC) to induce metabolic stress, in the presence or absence of succinate. Cellular response was determined by the measurement of intracellular ATP, extracellular metabolic markers (glucose, lactate, pyruvate, glutamate and glycerol), and oxygen consumption rate (OCR). The cultures showed metabolic flexibility, maintaining ATP levels in the presence of rotenone, possibly through glycogen stores in astrocytes and/or high glycolytic capacity. However, a metabolic deficit was observed in in the hours following rotenone administration, increasing the lactate/pyruvate ratio. The presence of succinate induced recovery from this metabolic deficit. The OCR of rotenone-treated cells also showed significant, immediate metabolic improvement in response to succinate. The results indicate that succinate can improve oxidative metabolism in mixed glia, consistent with our other observations in succinate-treated focal areas of injured human brain.



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Poster number: P-M074
Theme: Neuronal, glial & cellular mechanisms

Dopamine augments a tonic inward current in fast spiking interneurons in layer V of primary motor cortex

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Primary motor cortex (M1) has been implicated in the pathogenesis of Parkinson`s disease (PD) which is characterised by loss of dopamine neurons in the substantia nigra leading to loss of dopaminergic input to many brain regions. Recent studies have reported that dopamine (DA) controls tonic currents in medium spiny neurons, ventrobasal thalamus and nucleus accumbens by modulation of GABARs or cation channels. This study investigates the DA modulation of tonic currents in inhibitory interneurons in primary motor cortex (M1) in rats. Whole-cell voltage clamp recordings were made in deep layers (V) of M1 in sagittal brain slices (350 µm) obtained from male Wistar rats (50 g). FS interneurons and pyramidal neurons were identified by their characteristic shape and location. Application of DA (30 µM) induced a tonic inward current (-32 ± 8 pA, n=40). To investigate whether DA induced current was via GABAR, bicuculline (Bic; 20 µM) or picrotoxin (PTX; 50 µM) was bath applied. Itonic was partially (56%) reversed by both drugs (DA mean Itonic of -34 ± 7 pA was reduced to -21 ± 3 pA and -18 2 ± pA (when Bic (n=5, $p<0.01$) and PTX (n=5, $p<0.05$). All subsequent experiments were performed in the presence of Bic. The Bic-insensitive Itonic was found to be independent of Ih as DA increased Itonic in the presence of the HCN channel blocker, ZD-7288 (10 µM). Bath application of TRP channel antagonists, SKF96365 (100 µM) or 2-APB (100 µM) revealed a significant blockade of Bic-insensitive Itonic (mean amplitude of -26.4 ± 2 pA and -27.2 ± 7 pA reduced to -0.65 ± 1.8 pA and 1 ± 0.3 pA in the presence of 2-ABP and SKF96365 respectively, n= 5, $p<0.01$) suggesting a role of TRPc channels. These results suggest that there are two different types of tonic currents in FS cells in M1, one mediated via GABAR and another via non selective cationic conductance mediated by TRP channels.

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Poster number: P-M075
Theme: Neuronal, glial & cellular mechanisms

Role of leptin as a regulator of mitochondrial fission/fusion dynamics in vitro models of Alzheimer's disease

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The adipose hormone leptin has been revealed to play a neuroprotective role in cellular and animal models of Alzheimer's disease (AD). Recent studies indicate that the neuroprotective effects of leptin in AD models may be associated with improvement in mitochondrial functions. Mitochondrial dysfunction has a recognized role in the pathophysiology of AD. However, the mechanism of

leptin's protective effect on mitochondria in AD remains largely unknown. Mitochondrial fission and fusion are beneficial processes that promote mitochondrial distribution across axons into synapses, and separate damaged mitochondrial constituents, to meet high neuronal energy demand and facilitate protective effects. Our aim is to explore effects of leptin on mitochondrial dynamics in a serum-free cellular model and an amyloid-beta-induced AD model. In this study, we examined changes in mitochondrial morphology, oxidative stress, protein expression and cell viability following serum withdraw or amyloid-beta toxicity with or without leptin treatment. We documented the roles of mitochondrial fission and fusion proteins on mitochondrial biogenesis and morphology. In conclusion, leptin may facilitate neuroprotective effects through regulating mitochondrial fission/fusion dynamics in in vitro models of AD, which provides a novel insight into the mechanisms underpinning the neuroprotective effects of leptin.

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Poster number: P-M076
Theme: Neuronal, glial & cellular mechanisms

Regulating glycolysis: the relationship between activity and oligomeric state differs for each of the three phosphofructokinase isozymes

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Background:
Changes in brain glucose metabolism are found in many neurological diseases, including Alzheimer's disease, multiple sclerosis, epilepsy, and Down's syndrome. Phosphofructokinase (PFK) activity is a key regulator of glycolytic flux, with three isozymes (M, L, & P); each subunit is 85kDa. Studying PFK structure and function may help our understanding of how energy metabolism is disturbed in neurological illnesses. This study aimed to investigate how PFK activity relates to quaternary structure for each pure isozyme.

Methods:
PFK-deficient S. cerevisiae cells were transformed with plasmid pJJH71 containing cDNA for N-terminal His6 tagged PFK isozyme. Cells were lysed with liquid homogenisation and purified with immobilised metal ion affinity chromatography. Quaternary structure was assessed with size exclusion chromatography. PFK activity was quantified using a linked-enzyme assay.

Results:
Size exclusion chromatography showed material divided into three distinct size distribution peaks. PFK activity was near zero in peak 1, high in peak 2, and low in peak 3. Calculating specific activities showed the majority of active PFK was in peak 2.

The size distribution and shape of the active peak differed greatly between each isoform (figure 1). PFK-M was most active around 522kDa (hexamer); PFK-L at 870kDa (decamer); and PFK-P was much smaller, at 174kDa (dimer). SDS-PAGE gels showed PFK extended over a wide size distribution, especially PFK-L.

Interpretation:
These results indicate that PFK activity is dependent on oligomeric state with a different relationship for each isozyme. Additionally, each PFK has varying oligomeric stability, as shown by the breadth of the respective chromatography peaks. A rapidly shifting dynamic equilibrium between different oligomeric states may complicate analysis of oligomeric status; further biophysical studies will help answer this question. The suggestion that PFK-P has a different profile than the other isozymes is particularly intriguing as expression of this isoform is thought to be more brain-specific than the others. Understanding the differences between PFK isozymes and how brain expression of each isozyme differs in health and disease will help unlock some of the mysteries of brain metabolism.

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Poster number: P-M077
Theme: Novel treatments & translational neuroscience

Interfacing with the peripheral nervous system using mechanically compliant prostheses

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Neural interfaces allow the establishment of connections between the nervous system and external electronics, and hold great potential in both the clinic and basic research. The peripheral nervous system is a particularly attractive site to position an interface. Nerves are easy to access surgically and action potentials carried by them correlate well with activity at their target. Although many designs for peripheral nerve interfaces have been developed, they all face a major challenge upon chronic implantation.

Materials used in implants are orders of magnitude stiffer than most tissues, which tags them as foreign. As a result, the body responds to interface implantation with inflammation and fibrosis – a foreign body reaction – damaging the nearby fragile nervous tissue. This process is particularly detrimental in invasive implants which require penetration of the nerve's epineurial sheath, such as Utah arrays or microchannel-based implants [1].

In order to avoid this foreign body reaction, we have tested low-stiffness materials as potential components for neural interface manufacture. Polyacrylamide hydrogels with mechanical stiffnesses imitating those of peripheral nerves reduce fibrotic behaviour in nerve fibroblasts, compared to stiffer materials. These results suggest that low stiffness materials can be used to manufacture peripheral nerve interfaces which avoid the host foreign body reaction.

1. Chew, et al. Sci Transl Med 5, 210ra155–210ra155 (2013).

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Poster number: P-M078
Theme: Novel treatments & translational neuroscience

Monitoring the neurobehavioral and toxicological effects of the transition from smoking to e-cigarette use

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Electronic cigarettes (e-cigarettes) have proved very popular with smokers and a meteoric rise in their usage is currently being experienced. They are purchased as an aid to giving up smoking or to reduce cigarette consumption. Although the safety and impact on health of e-cigarettes has not been evaluated, they are generally considered to be far safer alternatives to traditional tobacco cigarettes. However, e-cigarettes also contain nicotine which is highly addictive. Consequently, it is imperative to ascertain the neurobehavioral effects of the transition from smoking to e-cigarette use as well as the toxicity risk (if any) of consuming nicotine through e-cigarettes. Our pilot study monitors levels of nicotine, cotinine and carcinogenic tobacco-specific nitrosamines in the urine, cortisol and DNA adducts in saliva and carbon monoxide in expired breath of heavy smokers who give up smoking and transition to e-cigarette use for a period of 4 weeks. Moreover, cigarette craving, mood, anxiety, social anxiety, sleep quality, blood pressure and heart rate are measured throughout to assess the psychological and cardiovascular effect of this transition. Finally, resting state brain electrical activity are measured by electroencephalography (EEG) and regional changes in activity monitored before and after the transition to e-cigarettes. Study compliance is monitored by expired carbon monoxide. Our tomographic analysis of the first EEG data from the subject has identified highly significant changes in regional activations throughout the brain between pre- and post- transition to e-cigarette use, but of course which of them, if any could be related to the change in smoking can only be ascertained after many more subjects are studied. Our preliminary behavioural data have revealed modest changes in nicotine craving, nicotine withdrawal symptoms, social anxiety and sleep quality following the transition to e-cigarettes. Slight changes in blood pressure were also observed. Overall, the results from this study will provide important information on the safety and effectiveness of e-cigarettes for smoking cessation which we anticipate will drive policy decisions with respect to e-cigarettes and their use.

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Poster number: P-M079
Theme: Novel treatments & translational neuroscience

Phase dependent modulation of epileptic activity in vitro using closed loop optogenetic control

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Epilepsy is a chronic disorder of the brain that affects an estimated 65 million people worldwide, and 30% of these cases are refractory to anti-epileptic medication. Refractory epilepsy patients can potentially be treated surgically but only a tiny minority of these become seizure free following surgery. The recent development of optogenetic technology provides an alternative strategy for epilepsy treatment with precise spatiotemporal control of targeting selective cells and neural circuits.

Experiments were performed using coronal brain slice preparations of neocortex from EMX-ChR2 and PV-ChR2 mice, selectively expressing channelrhodopsin-2 in either glutamatergic cells or parvalbumin-expressing cells (PV) respectively. Epileptiform activities were induced in slices by bath application of 4-aminopyridine 4-AP (200µM). Opsins were activated by using to a blue LED (473nm) with the light intensity being modulated using a custom-made close-loop (CL) controlling device. We studied the effects of a range of different CL filtering and phase-shifted algorithms applied to the LFP. Data were acquired using Spike2 and analysed with custom scripts written in Matlab.

We assessed whether continuous CL optical stimulation of either pyramidal cells or PV cells can modulate the ongoing pathological activity in the neocortical brain slices. Our results suggest optical stimulation of excitatory cells produces a phase-dependent modulation of seizure-like events (SLEs), where distinct phases reduce the duration of SLEs and reduce power in high gamma band range. In contrast, optical activation of PV interneurons failed to produce any modulation of epileptiform activity across any phases. Control experiments using amber light (565nm) failed to produce any epileptiform activity modulation in EMX-ChR2 brain slices.

Several studies have suggested the efficacy of on-demand optogenetic control of seizure activity. We propose that continuous closed-loop optical activation of excitatory cells in certain phase/frequency combination may be useful to modulate ongoing pathological oscillations and ameliorate seizure activity.

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Poster number: P-M080
Theme: Novel treatments & translational neuroscience

New mouse models for the study of P2X7 receptor signalling in epilepsy

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Epilepsy is a serious neurological condition that affects 1% of the population. In recent years there have been advancements made in the development of therapeutic targets to treat epilepsy, however these drugs only treat symptoms and roughly 30% of patients remain drug refractive. Recent studies have shown that neuroinflammation plays an important role in epileptogenesis due to the induction of pro-inflammatory cytokines such as interleukin 1β during seizures. It has been postulated that inflammation is driven by the P2X7 receptor (P2X7R), an ATP-gated ionotropic receptor. P2X7R is mainly expressed on microglia, however a neuronal localisation has also been suggested.

Our lab has shown that antogonism of P2X7R results in a reduction in seizure severity during prolonged seizures and reduces the epileptic phenotype in mice, and is neuroprotective. In order to fully understand the role played by P2X7R during seizure generation and epilepsy, we have developed a mouse model which overexpresses the P2X7R with a tagged green fluorescent protein. The main component of this project is the characterisation of this mouse.

To date, we have shown that there is a significant increase in cell death in the hippocampus of these mice. As mentioned previously, P2X7R plays a key role in inflammation and this has been supported by results to date. Increased mRNA levels of inflammatory markers are also seen in the overexpressing mice in comparison to wildtypes. Data also suggest that there are also increased levels of glutamate, the excitatory neurotransmitter, perhaps contributing to an increase in seizure severity which will later be analysed. Surprisingly, we found a decrease in P2X4R in the transgenic mouse which may represent a compensatory mechanism taking place

for the overexpression of P2X7R. P2X4R is also involved in inflammation, thus potentially contributing to the inflammatory state. Further work needs to be completed on other purinergic receptor subtypes.

Future work will analyse differences between wildtype and transgenic mice after status epilepticus and the overall epilepsy phenotype over the course of 14 days.

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Poster number: P-M081
Theme: Novel treatments & translational neuroscience

A Patient Derived iPSC Model of Neuropathic Pain: A Platform for Biomarker and Drug Development

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There is a clinical need for neuropathic pain (NP) drug development in modern medicine due to significant heterogeneity in current disease diagnosis in patients and a lack of effective treatments. Most current drug development methods to elucidate mechanisms in NP biology are established through rodent models with a high attrition rate of compounds. The progression in technology since the initial discovery by Yamanaka in 2006 in generation of induced pluripotent stem cells (iPSCs) from readily available somatic cells through exogenous expression of Oct4, Sox2, Klf4 and cMyc gives a platform to develop iPSC-derived in-vitro models for human diseases. A NP patient-derived iPSC model offers a potentially unlimited source of disease relevant cells to elucidate the aetiology of NP, as well as the development of NP biomarkers for the discovery of novel analgesics.

For our preliminary analysis, skin biopsies have been collected and iPSCs generated through reprogramming using the Cytotune Sendai 2.0 virus from fibroblasts isolated and cultured feeder-free in defined xeno-free Essential 8 medium. Neuronal lines are generated from iPSC lines using commercially available defined neuronal differentiation medias and novel small molecule differentiation inducers. The role of hypoxia in neuronal differentiation is being assessed from iPSC colonies in comparison to normoxia, and monitored through culture using a range of hypoxic (1-5% O2) conditions.

iPSC cell lines have been reprogrammed from fibroblast samples, and immunostaining with TRA-1-60 and Oct-4 has confirmed iPSC marker expression within colonies (Fig 1). Pluripotency potential of the iPSC colonies has been determined through trilineage marker identification of βIII-tubulin, α -fetoprotein and smooth muscle actin expression within generated embryoid bodies, and genomic stability of colonies has been assessed through karyotyping.

In conclusion, progress has been made in the aim to generate NP patient iPSC-derived neuronal cell lineages. Once neuronal lineages are established, we will assess the potential of novel NP biomarkers as a tool for the purpose of high throughput drug development, allowing a more rapid turnover of potential lead compounds into a more focused preclinical stage of drug development.

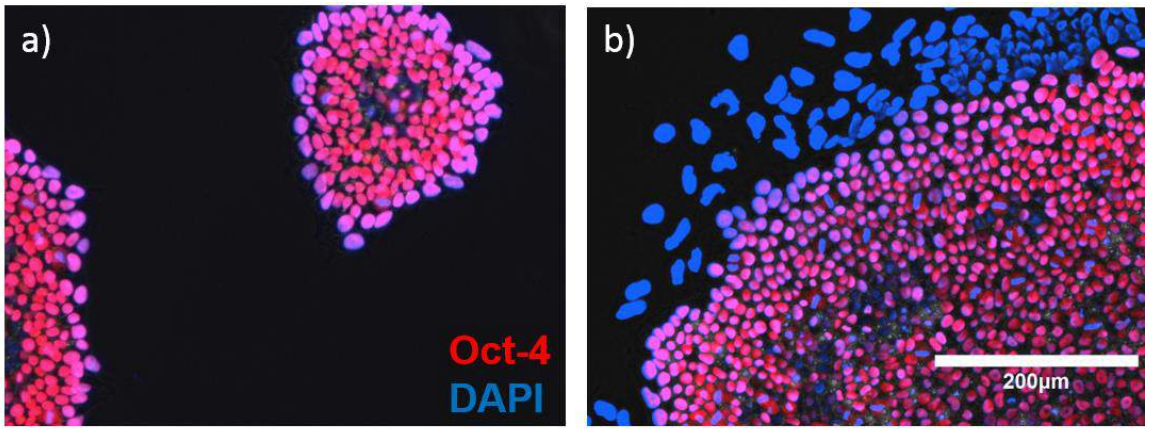

Fig 1: iPSC marker immunostaining of Oct-4 shown in P17 colonies (a) and differentiated cells lacking Oct-4 expression on colony periphery (b).

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Poster number: P-M082
Theme: Novel treatments & translational neuroscience

Efficient testing of treatment scenarios for brain disorders through large-scale computer simulations

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There are several approaches on how to improve brain function for brain disorders, ranging from drug application or behavioural therapies to surgery and brain stimulation. There are also several options within each approach, e.g. what drug to give or which part of the brain to surgically remove. Computational models can be used to inform the decision on the right approach and target in individual patients. Our hypothesis is that testing only a subset of all possible approaches is sufficient to discover treatment solutions which are near-optimal by maximising treatment effects and minimising side effects.

Using a computational model of brain activity, we attempt to predict the outcome of surgical resection in the human cortex. The aim is to identify the areas of the cortex which, when resected, adequately reduce seizure occurrence and minimise side effects for patients with epilepsy. Efforts have already been made to model surgery in the brain in the context of epilepsy, but our focus is on testing many possible interventions in a reduced amount of time.

Working towards this goal, we present a novel computational model of brain activity based on Hopfield networks. By using this simple model and applying techniques from game theory, we are able to quickly predict the outcome of many different resections. In contrast to other more complex models, the simplicity of the model also allows us to predict the resection outcome for networks consisting of many hundreds of regions of interest, providing increased granularity in resection planning.

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Poster number: P-M083
Theme: Novel treatments & translational neuroscience

The effect of a JmjC histone demethylase inhibitor, IOX-1, on proliferation and cell death in medulloblastoma cells

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In recent years, the JmjC histone demethylases have come into the spotlight as major modulators of histone methylation and gene expression. In particular, JmjC family members KDM6A/UTX and KDM6B/JMJD3, which demethylate lysine 27 on histone H3 (H3K27), have been shown to play a major role in neural differentiation (Jepsen et al., Nature, 2007). H3K27 methylation is critical in transcriptional gene repression and is implicated in many biological processes such as X-inactivation, genomic imprinting, stem cell maintenance, body patterning and cancer (Conway et al., Curr Opin Cell Biol, 2015).

Aberrant methylation of H3K27 can be found in around 25% of all medulloblastoma cases, and KDM6A/B are mutated in >50% of group 4 medulloblastomas, indicating aberrant methylation of H3K27 is contributory to a major fraction of this form of cancer (Dubuc et al., Acta Neuropathol, 2013). However, the functional roles of KDM6A and KDM6B in medulloblastoma cells remain unclear.

5-carboxy-8-hydroxyquinoline (IOX-1) is a recently discovered broad-spectrum 2-oxoglutarate oxygenase inhibitor with activity against the JmjC histone demethylases (Schiller et al., ChemMedChem, 2014). By examining the effect of IOX-1 on proliferation and cell death in the Daoy cell line, we hope to gain a better understanding of the cellular functional roles of KDM6A/B in medulloblastoma cells. At the same time, the potential value of IOX-1 as a drug candidate can be assessed.

In this study, Daoy cells were treated with IOX-1 at a range of concentrations (1, 5, 10, 50uM) and treatment durations (24h and 48h). Cell death and proliferation after treatment were investigated by trypan blue and EdU assays respectively.

IOX-1 showed a dramatic inhibition of cell proliferation at 50uM concentration, at both 24h and 48h treatment durations. Increased cell death was seen only at the highest concentration and duration tested (50uM, 48h). This points to a role for KDM6A/B in proliferative and possibly anti-apoptotic pathways in medulloblastoma progression. Further, as the effective concentration of IOX-1 found is 50-fold higher than that required to inhibit KDM6A in vitro, these results also indicate low cell permeability of IOX-1.

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Poster number: P-M084
Theme: Novel treatments & translational neuroscience

Mechanisms of inflammation and the role of dexamethasone in treating chronic subdural haematoma

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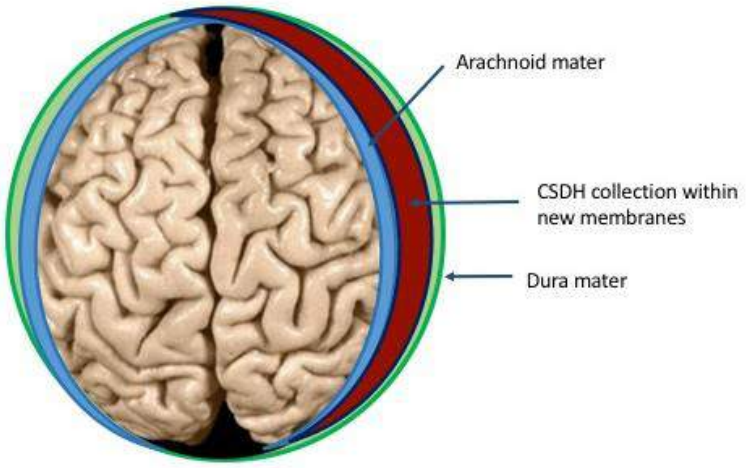
Chronic subdural haematoma (CSDH) is an encapsulated collection of fluid and blood that forms over the surface of the brain. It develops over weeks to months and is primarily seen in elderly patients. It is hypothesised to occur following trauma (overt or covert) to the head which disrupts the dural border cells layered between the arachnoid and dura mater. Inflammatory cells are then recruited to this region to attempt to repair this cell layer, but instead promote formation of fibrocellular connective tissue which forms a new membrane. Many of the inflammatory cells also have pro-angiogenic actions and therefore this membrane develops a complex network of fragile vessels. Through repeated micro-haemorrhage and fluid exudation from these vessels, a progressive CSDH collection develops.

CSDH is normally treated with surgical drainage, however the collection can recur and require multiple operations. An adjunctive therapy, dexamethasone, is being investigated as an anti-inflammatory agent to promote resolution of CSDHs following drainage. We are currently collecting peripheral blood and intra-operative CSDH samples from patients who have been randomised to dexamethasone or placebo treatment prior to surgical drainage. A Luminex assay is being performed to measure a range of inflammatory markers in the samples. This will consolidate current knowledge on the abundance of inflammatory markers seen in CSDH (e.g. IL-6, IL-8, VEGF) and include investigation of novel markers (e.g. MMP-9, MIP-1). Further to this a method has been developed using high performance liquid chromatography (HPLC) to analyse samples for presence and concentration of dexamethasone. This will enable us to understand whether dexamethasone penetrates directly into the subdural collection and its influence on the inflammatory markers being assessed. This study allows the first insight into the mechanistic actions of dexamethasone in relation to inflammation in CSDH.



Representation of anatomical location of a left chronic subdural haematoma (CSDH)

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Poster number: P-M085
Theme: Novel treatments & translational neuroscience

Novel peripheral histamine H3 receptor antagonist ZPL-868087 attenuates mechanical hypersensitivity in neuropathic pain in mice

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The histamine H3 receptor (H3R) is expressed in nociceptive pathways and our earlier studies identified H3R in A delta fibres. There is also growing evidence supporting a role for H3R in the modulation of mechanical pathological pain however many of the findings reporting the functional implication of H3R in chronic pain have been somewhat contradictory. Recent development of a selective and peripherally acting/centrally-sparing H3R ligand ZPL-8680872 has provided an interesting tool for further investigation of the role of H3R in nociception and validation of peripheral H3R as a potential target for therapeutic intervention in chronic pain. We therefore evaluated the analgesic efficacy of ZPL-868087 in peripheral neuropathic pain induced by chronic constriction injury (CCI) of the sciatic nerve in adult male C57BL/6J (B6) mice (n=6/group). The effect of ZPL-868087 (1, 3 and 10 mg/kg i.p.) on mechanical and heat hypersensitivity at the plantar surface of the hind paw was assessed using von Frey filaments and Hargreaves test and was determined 0.5, 1 and 24 h after each ZPL-868087 administration (4 injections every 24 h for 4 days). Treatment with 3 and 10 mg/kg resulted in alleviation of mechanical, but not heat hypersensitivity while 1 mg/kg was ineffective compared to controls. In a separate experiment, adult male B6 mice (n=5-8/group) were subjected to severe hyperglycaemia-induced hypersensitivity developed after a single streptozotocin (STZ, 200 mg/kg i.p.) injection. Here, the effect of ZPL-868087 (10, 30 and 100 mg/kg p.o.) on mechanical and cold hypersensitivity was assessed using von Frey filaments and the acetone test and was determined 1 and 24 h after each ZPL-868087 administrations (6 treatments every 24 h for 6 days). While all tested doses inhibited cold hypersensitivity, only 100 mg/kg inhibited mechanical hypersensitivity. None of the ZPL-868087 doses influenced nociceptive thresholds in control STZ animals. Our immunoblotting and immunohistochemistry studies indicated that ZPL-868087 analgesic effects were mediated through the extracellular signal-regulated kinases pathway. Together, this study emphasizes the importance of the H3R in the modulation of chronic pain and in alleviation of, in particular, peripheral neuropathies.

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Poster number: P-M086
Theme: Novel treatments & translational neuroscience

Anti-seizure and biophysical effects of microRNA-134 knockdown

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MicroRNAs (miRs) are ~22 nt non-coding RNA sequences, which typically suppress gene expression through specific binding to target mRNAs. MiR-134 is upregulated in multiple models of epilepsy and influences the density and volume of dendritic spines. MiR-134 knockdown protects against seizures, though it is unclear how. We explored the effects of miR-134 knockdown in naïve ex vivo brain slices.

Adult male Sprague Dawley rats were given intracerebroventricular injections of an ‘antagomir’ against miR-134 (ant-134). Rats completed a novel object location test at least 24 hours after injection and brain slices were prepared 2-4 days post-surgery. Anti-epileptic effects were tested by seizure challenge with 9 mM K+. Intrinsic biophysical neuronal properties were tested with whole cell voltage and current clamp. Recorded neurons were filled with biocytin for posthoc anatomical reconstruction.

Ant-134 significantly delayed the onset of epileptiform activity in 9 mM K+ by an average of 182 s relative to control (n = 9 control slices; 11 ant-134 slices; Mann Whitney U test p = 0.002). There was a tendency towards a faster action potential rising slope in pyramidal neurons though this did not pass significance after correction for multiple comparisons (control: 179 ± 82 mV/ms, n = 6 neurons; ant-134: 251 ± 18 mV/ms, n=7 neurons; independent samples t test p = 0.043, α=0.025). Preliminary analysis also suggested a counterintuitive increase in mEPSC frequency in response to ant-134. These results will be substantiated and correlated with effects on neuronal morphology and rats’ performance in the spatial memory test.

We have replicated the anti-seizure effects of ant-134 in an acute model of epileptiform activity, showing that the anti-epileptic effect can be produced in healthy brain tissue. We saw little or no effect of ant-134 on many biophysical parameters, suggesting it mediates seizure resistance through relatively specific mechanisms, which could be valuable for future translation to the clinic.

This work was supported by the EpimiRNA consortium and a fellowship from the Royal Society.

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Poster number: P-M087
Theme: Novel treatments & translational neuroscience

Epilepsy-associated GRIN2A mutations – functional analysis and pharmacological rescue of phenotypic deficits

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The epilepsy-aphasia spectrum (EAS) represents a continuum of genetic epilepsy syndromes with the EEG signature of focal sharp waves, concurrent with various speech and language disorders. They range from the frequent focal epilepsy Rolandic epilepsy, to the severe epileptic encephalopathies Landau-Kleffner syndrome (LKS) and continuous spikes and waves during slow-wave sleep (CSWS). Around 20% of cases in this spectrum are caused by mutations in the NMDA receptor GRIN2A. Using bioinformatic and patient data we shortlisted 10 diverse missense mutations for characterisation and investigate strategies for restoration of functional deficits. Human GRIN2A mutation constructs were transiently transfected into HEK-293 cells along with GRIN1 to form heterotetrameric receptors. Confocal imaging of immunolabelled cells showed normal membrane expression for wild type (WT), however protein from two GluN2A mutants were not trafficked to the cell membrane, and another three mutants had significantly reduced levels of membrane expression. Western blotting revealed mutations before the C-terminal domain of the NMDAR had vastly reduced total expression compared to WT, with those that disrupt the disulphide-bond of cysteine residues expressing less than 50% of WT protein levels. Single cell calcium imaging and patch clamp recordings showed that mutations both at the interface of GluN1 and GluN2A and close to the glutamate binding site caused a significant reduction in glutamate and glycine potency, with two mutants producing non-functional proteins. Mutations located after the glutamate binding domain responded as wild-type to agonists. High-throughput calcium flux assays showed that all studied mutations do not appear to alter NMDA receptor antagonist pharmacology. We were able to rescue the phenotype of the mutations with reduced glutamate affinity after treatment with an GluN2A-selective positive allosteric modulator. We show that mutations across GRIN2A affect the expression and function of the receptor in different ways, with the end result of altered NMDA receptor currents and neuronal excitability. Careful molecular profiling of these patients is essential for effective personalised treatment options.

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Poster number: P-M088
Theme: Novel treatments & translational neuroscience

Identification and validation of biomarkers of neuropathic pain

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In 2014, it was reported that neuropathic pain (NP) had a prevalence in the population of 7%-10%. With analgesics having an efficacy of ~30%, there is a distinct lack of effective medication available to patients. This is further compounded with a growing and ageing population and thus NP is fast becoming a significant clinical issue that requires urgent attention. Due to the complex nature of NP and ill-defined pathophysiology of the condition, identification of robust biomarkers is perhaps more challenging than for other diseases. Our aims are to identify and validate molecular and genetic biomarkers of NP. We also look to determine drug targets of NP for development of more effective analgesics.

Peripheral blood samples were collected from healthy volunteers and patients with chronic neuropathic pain (>6 months). Patient samples were selected based on an S-LANSS score of >12. A pilot sample set (n=20) and validation sample set (n=100) was selected and RNA extracted from PAX RNA tubes. Samples were analysed using the Human Transcriptome Array 2.0 system to determine expression levels of RNA species. Expression values with a significant differential expression ($p \leq 0.05$) vs control were analysed in the ingenuity pathway analysis (IPA) software.

Analyses identified several differentially regulated gene candidates involved in the immune system in patients with NP. These included the downregulation of the cytokine receptor CX3CR1 (Log ratio -0.480) and the killer cell receptor KLRB1 (Log ratio -0.633). We further explored whether there were distinct expression patterns through an IPA analysis of our array data. This identified that the observed differential regulation in NP is indicative of the depletion of immune cells.

These results suggest that the loss of immune cells in blood may contribute to the persistence of NP over an extended period of time through genetic pathways not yet identified. As NP does not occur in all patients following trauma or lesion of the CNS, it could be hypothesised that a lack of immune cells in a subset may lead to the presence of NP long after the aetiological cause has disappeared. In summary, this study has laid the groundwork towards the discovery of biomarkers relating to NP, which will be further explored in future research.

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Poster number: P-M089
Theme: Novel treatments & translational neuroscience

The purinergic P2Y1 receptor as novel target to treat status epilepticus

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Epilepsy is a chronic neurological disease characterized by recurrent seizures. Despite the existence of numerous AEDs, 30-40% of patients do not respond to treatment, showing the urgent need for novel therapeutic strategies. ATP, an important signaling molecule in the CNS, has emerged as a potential contributor to seizures. Purinergic P2Rs, comprised of ionotropic P2XRs and metabotropic P2YRs, are expressed in the brain and activated by ATP. The majority of studies in epilepsy have been focus on the P2XR subtype; however P2YRs are now emerging as potential new targets. Among the P2Y1R has been shown to be strongly expressed in astrocytes, where they contribute to the propagation of calcium waves. However, the functional role of P2Y1R during seizures is poorly understood.

The expression levels of P2Y1R after SE and the effect of P2Y1R on seizures, neuronal death and inflammation were studied using two different mouse model of epilepsy. Seizures were induced by intra-amygdala kainic acid or intraperitoneal pilocarpine injections in mice. P2Y1R expression was analyzed in whole hippocampus at different time points and in the hippocampal subfields after SE in mice. In addition, specific P2Y1R ligands were administrated into the ventricle after seizure induction and electroencephalography was recorded to assess seizure severity. Procedures were approved by the relevant Research Ethics Committees of the RCSI.

Protein levels of P2Y1R were up-regulated in the hippocampus after SE, mainly in DG and CA1. In contrast expression of P2Y1R is reduced in CA3 and is showing reduced reactivity in the mossy fibers of CA3 region in the KA model after SE. Our results in the KA model revealed that mice post-treated with P2Y1R specific agonist MRS2365 showed an increase in seizure severity, neuronal death and inflammation, while post-treatment with P2Y1R specific antagonist MRS2500 decreased seizure severity, neuronal death and inflammation. The same results were observed in the pilocarpine model, selling out model-specific effects. In conclusion, SE induces an increase in the P2Y1R in the whole hippocampus. P2Y1R inhibition might be a good approach for the treatment of SE and prevention of seizure-induced brain damage.

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Poster number: P-M090
Theme: Novel treatments & translational neuroscience

Spatiotemporal progression of ubiquitin-proteasome system inhibition after status epilepticus suggests protective adaptation against brain damage

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The ubiquitin-proteasome-system (UPS) is the major intracellular pathway leading to the degradation of unwanted and/or misfolded soluble proteins. This includes proteins regulating cellular survival, synaptic plasticity and neurotransmitter signaling; processes controlling excitability thresholds that are altered by epileptogenic insults. Dysfunction of the UPS has been reported to occur in a brain region- and cell-specific manner and contribute to disease progression in acute and chronic brain diseases.

Prolonged seizures, status epilepticus, may alter UPS function but there has been no systematic attempt to map when and where this occurs in vivo or to determine the consequences of proteasome inhibition on seizure-induced brain injury.

To determine whether seizures lead to an impairment of the UPS, we used a mouse model of status epilepticus whereby seizures are triggered by an intraamygdala injection of kainic acid. To monitor seizure-induced dysfunction of the UPS we used a UPS inhibition reporter mouse expressing the ubiquitin fusion degradation substrate ubiquitinG76V-green fluorescent protein. Treatment with the specific proteasome inhibitor epoxomicin was used to establish the impact of proteasome inhibition on seizure-induced pathology.

Our studies show that status epilepticus induced by intra-amygdala kainic acid causes select spatio-temporal UPS inhibition after seizures, which is, surprisingly, most evident in damage-resistant regions of the hippocampus, including CA1 pyramidal and dentate granule neurons then appears later in astrocytes. In support of this exerting a beneficial effect, injection of mice with the proteasome inhibitor epoxomicin protected the normally vulnerable hippocampal CA3 subfield from seizure-induced neuronal death in the model.

These studies reveal brain region- and cell-specific UPS impairment occurs after seizures and suggest UPS inhibition can protect against seizure-induced brain damage. Identifying networks or pathways regulated through the proteasome after seizures may yield novel target genes for the treatment of seizure-induced cell death and possibly epilepsy.

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Poster number: P-M091
Theme: Novel treatments & translational neuroscience

MicroRNAs as Novel Biomarkers for the Diagnosis and Prognosis of Traumatic Brain Injury

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Traumatic brain injury (TBI) is the leading cause of death and disability under the age of 45 years in Western countries. Despite many studies, no reliable biomarkers have been found to assess its severity and predict the recovery. MicroRNA (miRNA) profiling has become widely used to identify biomarkers and therapeutic targets.

The expression of 754 miRNAs was analysed in serum of 5 mild TBI (mTBI) with extra-cranial injury (EC) patients, 5 severe TBI (sTBI) with EC patients and 5 healthy volunteers (HV) at 1 day and 15 days post injury, by using the TaqMan® Array Human MicroRNA A+B Cards. The aim was to find candidate biomarkers able to discriminate between mild and severe TBI and assess the recovery from mTBI. Following this, it was possible to select 10 miRNAs for further study in an enlarged validation cohort of 120 patients by using single TaqMan assays at the following time points: T0-1h, T4-12h, T48-72h and 15 days from the injury.

Analysis revealed 2 miRNAs (miR-425-5p, miR-502) significantly downregulated ($p<0.05$) in mTBI at early time points and ideal candidates for diagnosis and monitoring the recovery; two miRNAs (miR-21 and miR-335) significantly upregulated ($p<0.01$) and valid biomarkers for the diagnosis of sTBI. In addition, miR425-5p and miR21 at time 0-1h were strongly predictive of 6-month outcome.

The panel of selected miRNAs shows promise as biomarkers to discriminate mild from severe TBI and to monitor the recovery from TBI. In addition, the selected miRNAs represent new potential therapeutic targets.

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Poster number: P-M092
Theme: Neurodegenerative disorders & ageing

Aging reveals qualitative differences in the watermaze performance of rats and mice

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The aging process is associated with cognitive decline in several species, and is a primary risk factor for neurodegenerative disease. Greater understanding of the comparative effects of aging is important for determining how to successfully interpret such results in a translational neuroscience context.

In this study, the watermaze was used to assess the spatial working memory performance of young male Sprague Dawley rats (11 mo, n=12) and C57Bl/6J mice (3 mo, n=12) with that of old animals (rats: 24 mo, n=12; mice; 26 mo, n=12). All animals were tested in the same pool under the same conditions. Initially, subjects received spatial cue training to test acquisition of hidden platform location. Platform location remained fixed while start location was randomised. A trial was successfully completed when an animal dwelt on the platform for 5 s, otherwise the trial stopped after 90 s. All animals received 4 trials per day. Following this, one probe trial was administered to assess memory retention. Finally, 4 trials of visual cue training utilising a visual platform was administered.

Visual task performance was normal in all animals. Young rats and mice successfully learned the spatial task in an equivalent manner, and demonstrated memory retention during the probe trial. While aged rats took longer to complete the spatial task than young animals, they maintained a significant but decreased target quadrant preference during probe. In contrast, aging had no effect on escape latencies in mice during the spatial task; yet old mice demonstrated no significant target quadrant preference during probe. A time dependent decrease in thigmotaxis was seen in young rats and all mice, irrespective of age. Aged rats did not exhibit thigmotaxis to any degree.

This work showed that, under identical training conditions, watermaze performance declined in a qualitatively different manner as a function of age in rats and mice. Based on thigmotactic patterns, a stress/anxiety component may differentially contribute to deficits. As watermaze testing is often used as a “gold standard” spatial memory task in preclinical neurodegenerative research, some caution may therefore be required in the interpretation of datasets measured over longer lifespans in each species.

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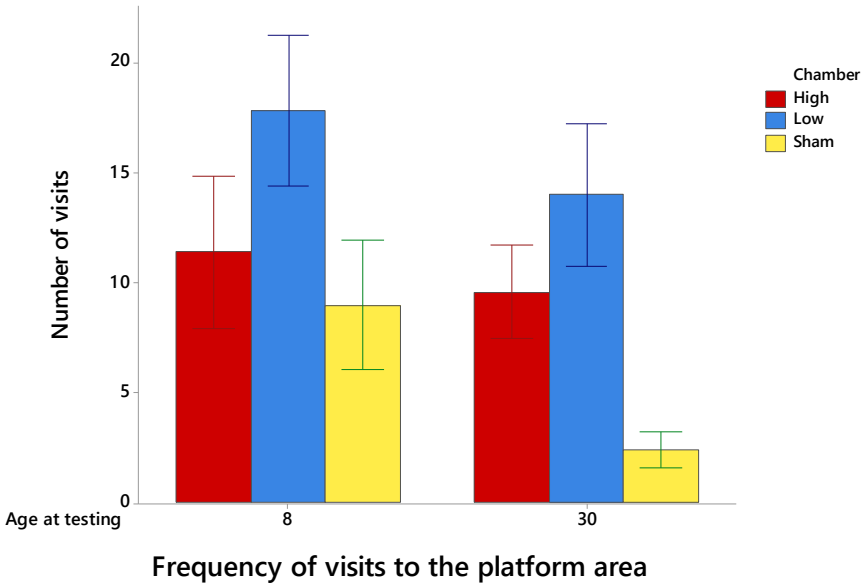
Poster number: P-M093
Theme: Neurodegenerative disorders & ageing

The effects of radiofrequency field exposure on neurodegeneration in a Senescence Accelerated Mouse model

Authors: Amelie Gavard - *Centre for Radiation, Chemical and Environmental Hazards Public Health England*

Despite much research, it remains unclear whether long term exposure from the radiofrequency (RF) fields associated with mobile phone use has an effect on brain function. Previous studies have shown an effect of RF fields on learning and memory in some animal models. We investigated the impact of repeated exposure on spatial learning and memory in the SAMP8 mouse which is a Senescence Accelerated Mouse model. Histologically, this model shows signs of Alzheimer’s disease with neuron atrophy and loss, an increase in oxidative damage, astrogliosis and an activation of microglia. This model also shows an age-related increase in senile β-amyloid plaques. In this study, male mice aged 8 weeks old were exposed to pulsed 1800 MHz fields for 30 minutes per day, 5 days per week for 2 months. The mice were randomly divided in 3 groups, and exposed at whole-body average specific energy absorption rates of 3 W.kg-1(High), 0.3 W.kg-1 (Low) or 0 W.kg-1 (Sham). At 8 weeks of age, a probe trial in the Morris water maze task showed no significant difference in memory retention between the exposure groups. Animals were retested at 30 weeks of age, and while there were no significance differences between the different groups in swim velocity or time spent in the platform zone, there was a significant increase in the number of visits to the platform zone between the exposure groups (ANOVA, $p<0,02$). Post hoc testing revealed that an exposure to 0.3W/kg (low) resulted in an increased number of visits to the platform zone when compared to sham exposed mice ($p<0.02$). Although exposure to 3W/kg (high) also resulted in an increased number of visits this was not significant when compared to sham exposed animals. Our results suggest that exposure to a low RF field can improve spatial memory in an aged mouse model. Immunohistochemistry for β-amyloid and neuronal loss is currently underway to investigate the potential underlying mechanism for the change in spatial memory.



Frequency of visits to the platform area

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Poster number: P-M094
Theme: Neurodegenerative disorders & ageing

CYFIP2: Altered local protein synthesis links A-beta production,tau hyperphosphorylation,spine abnormalities and memory impairment

Authors: Anshua Ghosh, Karl Peter Giese, *Basic & Clinical Neuroscience King's College London*

Alzheimer's disease (AD) is characterised by the presence of amyloid-beta (A-beta) plaques and tangles comprising hyperphosphorylated tau.However it is in fact synaptic degeneration that best correlates with the memory impairment and precedes neuronal loss.Therefore early changes in the AD brain may involve alterations at synaptic sites.These localised changes require rapid access to specific macromolecules and an attractive hypothesis is that several proteins required for synaptic function are locally synthesised within dendrites or spines,and are regulated by RNA-binding proteins and related molecules.A likely candidate for such local protein synthesis is the Cytoplasmic FMRP-Interacting Protein 2 (CYFIP2),a highly conserved protein that is abundant in synapses.While not much is known about the precise physiological role of CYFIP2 in the brain,it has been proposed to have functions in regulating protein synthesis of FMRP-regulated mRNAs,as well as in modulating cytoskeletal dynamics via a Rac-dependent pathway.We have previously found that CYFIP2 is reduced by about 50% in severe AD post mortem hippocampus when normalised for the number of synapses,suggesting it is an early event that precedes synaptic loss.Adult CYFIP2 heterozygous knockout mice have been used to model the condition.At the biochemical level,CYFIP2+/- mice have increased expression of FMRP-regulated proteins such as Amyloid Precursor Protein (APP) and the alpha subunit of the calcium/calmodulin-dependent kinase II (aCaMKII) at hippocampal synapses.CYFIP2+/- mice also have increased levels of the APP-cleaving enzyme Beta-secretase 1 (BACE1) in hippocampal synapses,and elevated Abeta 1-42 in whole hippocampi.Additionally there is increased tau phosphorylation in hippocampal synapses at Ser214,a site that is phosphorylated by aCaMKII in the AD brain and known to result in dissociation of tau from microtubules in vitro.These mice also have altered spine morphology in hippocampal CA1 neurons and impaired retention of spatial memory in the Morris water maze.Taken together,reducing CYFIP2 in the mouse brain is sufficient to recapitulate key aspects of the disease.Further studies will be done to study the impact of CYFIP2 reduction on different brain regions.

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Poster number: P-M095
Theme: Neurodegenerative disorders & ageing

Cell/cell transmission of LRRK2

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Both humans and flies have dopaminergic neurons in their visual system. Humans with Parkinson's Disease (PD) lose the tyrosine hydoxylase staining in amacrine cells, and show visual deficits, while flies that express the PD-related gene Lrrk2-G2019S in dopaminergic neurons lose visual transduction and show degeneration of the photoreceptors. Since fly photoreceptors use histamine, rather than dopamine, as their transmitter, this implies cell/cell signalling.

dLRRK loss of function mutants show a deficit in signalling in the fly retina, though photoreception is unaffected. This deficit is recused by expression of dLRRK, hLRRK2, LRRK2-G2019S or even mLRRK1 in the dopaminergic neurons. Curiously, expressing these transgenes in the glial neurons is nearly as effective as neuronal expression. Again, this suggests cell/cell signalling.

Although dLRRK mutants and white-eyed mutants are both viable, when the dLRRK mutation is transferred into a white-eyed background no flies are found: the double mutant is lethal. Conversely, when the gain of function mutation LRRK2-G2019S is expressed in a white-eyed fly, neurodegeneration is prevented. These observations suggest a strong reciprocal interaction between LRRK2 and eye pigment pathways.

Since flies have no α-synuclein and mammalian kidneys excrete LRRK2 in exosomes, our data may be interpreted by an exosome mediated transfer of LRRK2 between neurons, photoreceptors and glia. Lysosomes are linked to production of the red/brown pigment granules in the fly eye, as well as to exosomes. As fly pigment granules, like melanosomes, are lysosomal-related organelles, our data provide an explanation for the high sensitivity of dopaminergic neurons to PD.

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Poster number: P-M096
Theme: Neurodegenerative disorders & ageing

What is the role of the WDR45 gene in autophagy?

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Autophagy is a cellular process involved in the turnover of materials and subcellular structures. WDR45 is a protein with a putative role in autophagy regulation, and mutations in WDR45 lead to disease. The function of the WDR45 protein has not been fully elucidated, and it is the focus of our investigations. It may act as a regulator of autophagy, possibly behaving as the scaffold for proteins involved in early autophagy to assemble. Patients with de novo WDR45 mutations are diagnosed with BPAN: beta-propeller protein associated neurodegeneration.

MRI scans of BPAN-patient brains exhibit iron accumulation in the substantia nigra and globus pallidus and generalised atrophy of cerebrum and cerebellum. Post-mortem brain sectioning reveals neurofibrillary tau tangles throughout the cortex, with mixed 3R-4R pathology similar to Alzheimer's disease. Certain mutations in WDR45 have also been implicated in Rett-like syndrome and epilepsy, further highlighting the implications of our project to neurodegenerative research at large.

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

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

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Poster number: P-M097
Theme: Neurodegenerative disorders & ageing

Acyl-ghrelin regulates mid-brain mitochondria and protects neurones in an in-vitro rotenone-based Parkinson's disease model

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Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder in humans. It is characterised by the progressive loss of the A9 (Girk2+) subpopulation of dopamine (DA) neurones in the Substantia Nigra Pars Compacta (SNpc). The majority of PD cases are idiopathic. However, environmental toxins that inhibit the mitochondrial electron transport chain cause PD-like symptoms and recent studies of rare familial PD implicate metabolic dysfunction as a possible cause of DA nerve cell loss. We propose that the homeostatic hormone, acyl-ghrelin, may prevent DA neurone loss by preserving nerve cell metabolism during bioenergetics stress.

Methods;
In the in-vivo MTPT and 6-OHDA-toxin model of PD acyl-ghrelin prevents SNpc DA neurone loss in an acyl-ghrelin receptor (GHSR)-dependent manner. Here, using the eGFP-GHSR reporter mouse we demonstrate co-localised expression of the GHSR with TH+ and Girk2+ SNpc neurones. This suggests that acyl-ghrelin may exert a direct protective effect on A9 DA neurones via GHSR+ signalling. Using a mouse-midbrain-derived neuronal cell line (SN4741), immunopositive for TH+/ Girk2+/GHSR+, we assess the neuroprotective potential of acyl-ghrelin in an in-vitro rotenone-based PD model. High-Content Screening and Super Resolution microscopy (SIM) approaches were utilised to investigate mitochondrial health and morphology in dopamine neurones in-vitro.

Results;
• Acyl-ghrelin promotes phosphorylation of the cellular energy sensor AMPK and ACC, suggesting a switch to fatty acid oxidation as an energy source in neurones during energetic stress
• Rotenone-induced TH+-neurone loss is greater when cultured in nutrient-restricted medium
• Acyl-ghrelin pre-treatment significantly attenuates rotenone-induced TH+-neurone loss
• Acyl-ghrelin prevents mitochondrial membrane potential and fragmentation loss during rotenone-induced mitochondrial stress
• Rotenone increases mitochondrial fragmentation (fission) marker Phospho-DRP1 in dopamine neurones in-vitro

Conclusions;
Acyl-ghrelin activates cellular pathways associated with protecting neurones against energetic stress and promoting healthy aging. These data suggest that ghrelin may be a potential therapy for protecting against PD progression.

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Poster number: P-M098
Theme: Neurodegenerative disorders & ageing

Immersive VIrtual Reality Testing of Entorhinal Cortex and Hippocampal function in ageing and Mild Cognitive Impairment (VIRTECH-MCI)

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Background. The entorhinal cortex (EC) is the first region to show neurodegeneration in Alzheimer's disease (AD). As such, detection of EC dysfunction will aid diagnosis of AD in its pre-dementia stages and stratification of individuals for future interventional therapies aimed at slowing the progression of disease.

The demonstration that EC cells have spatially related firing patterns (head direction cells and grid cells2) underpins the role of this region in spatial navigation.

To test the hypothesis that navigation is impaired in pre-dementia AD, this study used a novel immersive virtual reality (iVR) platform to test navigation within a simulated environment. The vestibular and locomotor feedback associated with the real world movement required for this iVR task delivers a more naturalistic paradigm than traditional "desktop" VR tasks. Prior to patient testing, normative data from older control participants have been collected and are detailed below.

Methods. Thirty control participants (aged 49-75, mean age 61, 17 female) were recruited from Join Dementia Research. All underwent multimodal MRI including whole brain volume, multiband resting state fMRI, diffusion tensor imaging and high resolution T2 acquisitions through the hippocampus with 0.4x0.4x2mm voxel size. The iVR environments consist of differing 4x4 metre arenas with boundary cues projected to infinity. Navigation was tested using a path integration paradigm in which participants sequentially walk up to, and "collect", three objects before being asked to return to the location of object 1 (figure 1). 9 trials were undertaken in each of three different environments, with three different conditions for the return path (boundary cues present, boundary cues absent, removal of ground details to disrupt optic flow). Performance is measured in terms of the distance between the estimated and actual location of Object 1.

Mean displacement errors for the three return conditions were as follows. No environmental change, 30cm (S.D: 32cm); no boundary cues 26cm (S.D: 27cm); no ground details 34cm (S.D: 34cm). ANOVA did not reveal a significant effect of return condition on performance [F (2, 376) = 1.71, p=0.18].

These data will be used as normative data for future

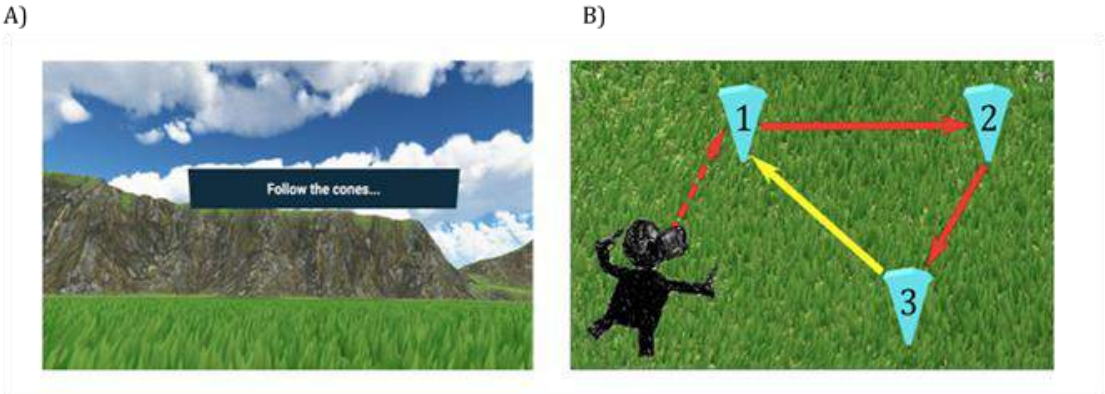

Figure 1. A) Example of what participants see in the virtual world. B) Abstracted birds eye view of the sequential collection of flags (red arrows). Return path (flag number 1 is always absent) is indicated by the yellow arrow

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Poster number: P-M099
Theme: Neurodegenerative disorders & ageing

Investigating the task-relevance of visual fixations during locomotion in Parkinson's disease

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Introduction: People with Parkinson's disease (PD) commonly report visual problems, such as impaired eye movements [1,2]. Visual dysfunction can impact safe walking capability, particularly if task-relevant visual information is not gathered when walking. Limited research exists that has explored the location of gaze fixations when walking [3], which are important for appropriate visual input during locomotion.

Aim: This study aimed to examine the task-relevance of fixation locations during various walking tasks in PD.

Method: 40 control (68.8[8.8]y, 20m) and 38 PD participants (69.6[8.2]y, 23m) ; one with no additional stimuli and another with additional stimuli (either with visual cues or a high contrast obstacle to transverse) whilst wearing a mobile eye-tracking device. All walks were repeated under dual task (Wechsler digit span) conditions. The location of fixations was manually classified, coded as relevant/irrelevant to the task, and analysed using negative binomial regression.

Results: During single task walking, people with PD made significantly more fixations (p=.032) with the difference resulting from more irrelevant fixations (p=.014). Both groups had similar number and relevance of fixations with visual cues (p=.359). However, people with PD required more task-relevant fixations (i.e. looked at the obstacle/floor more) to complete both single task (p=.007) and dual task (p=.007) obstacle crossing trials.

Conclusion: People with PD make more irrelevant fixations than controls when walking, which may contribute to impaired mobility and falls. High contrast obstacles and visual cues attract visual attention to relevant areas when walking, which may reduce falls risk. An increased frequency of task relevant fixations during both single and dual task obstacle negotiation indicated that home based modifications such as improving the salience of trip hazards may redirect visual exploration even when attentional demands are high. Further work is required to examine fixations locations when walking in real-world environments which contain more visual distractors.

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[3] Stuart et al., (2016). Neurosci Biobehav Rev, 62,p.76-88

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Poster number: P-M100
Theme: Neurodegenerative disorders & ageing

Precise modelling of inherited motor neuron disease using novel CRISPR/Cas9 technology

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Hereditary spastic paraplegias (HSPs) are a group of inherited conditions which primarily affect the longest motor neurons in the corticospinal tract. As a result, patients exhibit lower limb spasticity and muscle weakness. Though extremely heterogenous, the most prevalent cause of HSP arises from pathogenic variants in genes that encode endoplasmic reticulum (ER)-shaping proteins. Our lab has shown that loss of the ER-shaping proteins, Arl6IP1 and Reticulon-like 1, in Drosophila melanogaster disrupts ER organisation (Fowler & O'Sullivan, 2016). Additionally, loss of these proteins alters mitochondrial organisation and a loss of mitochondria from the distal ends of long but not short motor neurons. The ER is known to regulate mitochondrial division and our lab has found that upregulation of a mitochondrial fission protein, Drp1, restores mitochondrial organisation and ameliorates locomotor deficits associated with ER-shaping protein loss. However, the mechanism by which genetic variants cause this disruption remains unknown.

I am generating the first precise in vivo model of HSP using CRISPR/Cas9 gene editing in Drosophila melanogaster. Such models, expressing disease-causing genetic variants at endogenous levels, will provide a tool to investigate the effect of their respective proteins on ER-mitochondrial interactions in neurons. For example, I will use an existing live mitochondrial trafficking assay to examine mitochondrial transport in terms of anterograde and retrograde speed as well as total mitochondrial movement to determine if these rare models exhibit mitochondrial transport defects similar to other HSP models.

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Poster number: P-M101
Theme: Neurodegenerative disorders & ageing

Antidiskynetic effect of neuronal nitric oxide synthase inhibitor on L-DOPA Parkinsonian animals: is astrocyte a key element?

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Inflammation in Parkinson's disease (PD) is a new concept that has gained ground due to the potential of mitigating dopaminergic neuron death by decreasing inflammation. The solution to this question is likely to be complex. We propose here that the significance of inflammation in PD may go beyond the nigral cell death. The pathological process that underlies PD requires years to reach its full extent. A growing body of evidence has been accumulated on the presence of multiple inflammatory signs in the brain of PD patients even in very late stages of the disease. Astrocytes contribute to virtually all neuropathological conditions. Astrogliosis is an important component of cellular pathophysiology and its suppression generally aggravates neuropathology. The actual role of astrocytes in PD remains uncertain because these cells can both facilitate and prevent neuronal damage. Our recent results of L-

DOPA-induced dyskinesia in rodents correlates to significant findings regarding astrocytes and neuroinflammation. We also showed that in the rat model of PD/L-DOPA-induced dyskinesia there was an increased expression of inflammatory markers, such as the enzymes COX2 in neurons and iNOS in glial cells, in the dopamine-denervated striatum. Striatal COX2 co-localised with cholineacetyltransferase, calbindin and DARPP-32 (dopamine-cAMP-regulated phosphoprotein-32), neuronal markers of GABAergic neurons. NOS inhibition prevented L-DOPA-induced dyskinesia iNOS, GFAP, OX42 and COX2 increased expression in the dorsal striatum. The gliosis commonly seem in PD was associated with modifications in astrocytes that occured after chronic treatment with L-DOPA. The described inflammatory reactions were almost absent in rats with 6-OHDA-lesion, without L-DOPA treatment. Either as a cause, consequence, or promoter of progression of neuronal degeneration, astrocytes and inflammation played a role in PD. PD research ought to be to elucidate (i) the time sequence in which the astrocytes act in PD patient brain and (ii) the mechanisms by which astrocyte response contributes to the collateral effects of L-DOPA treatment.

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Poster number: P-M102
Theme: Neurodegenerative disorders & ageing

Acute effects of systemic inflammation upon neurovascular unit and neurovascular function

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Neuroinflammation, a chronic or acute inflammatory process within the central nervous system is a ubiquitous characteristic of many neurodegenerative diseases including Alzheimer's disease. The precise relationship between inflammatory processes and disease progression is complex and far from understood, but evidence from animal and human studies suggests that inflammation plays an important role in the developing neuropathology. Inflammatory processes are mediated by the cells of the extended neurovascular unit, which is also the substrate for the precise regulation of brain blood flow in accordance with local tissue requirements. An important question therefore is whether and how the effects of inflammation on neurovascular unit function impact upon neurovascular coupling. Furthermore, it is important to determine how changes that occur at the cellular level in inflammation impact upon blood flow regulation in-vivo.

To investigate this, we induced systemic inflammation in an acute rodent model in which cerebral blood flow (CBF), neuronal activity and haemoglobin oxygenation and concentration were measured to quantify the effects of inflammation upon haemodynamic responses and neurovascular coupling. In anaesthetised animals, a thin cranial window was prepared over the left somatosensory barrel cortex to enable recording of CBF using laser speckle contrast imaging as well as haemoglobin oxygenation and concentration with optical imaging spectroscopy. A surface electrode was placed adjacent to the window for neuronal activity recording. Data were acquired at two time intervals after lipopolysaccharide (LPS, 2mg/kg i.p) or vehicle (saline) administration. The brains were subsequently extracted for immunohistochemistry (IHC) to discern microglia, astrocytes, ICAM-1 and AQP4 expression.

In LPS treated animals. IHC findings indicate increased expression of astrocyte (GFAP) and microglial (IBA-1) markers, alongside increased ICAM-1 and AQP4 expression. In-vivo measurements reveal a rapid alteration of haemodynamic function as early as 6 hours post treatment. These findings have implications for fMRI experiments involving subjects/patients with an underlining systemic inflammation and for understanding how neurovascular function changes in systemic disease.

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Poster number: P-M103
Theme: Neurodegenerative disorders & ageing

Early dysfunction of glycinergic premotor neurons in a zebrafish model of amyotrophic lateral sclerosis

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Amyotrophic lateral sclerosis (ALS) is an untreatable orphan disease that causes degeneration of motor neurons, usually culminating in death within 2-3 years of diagnosis. Although ALS has traditionally been considered an acute-onset disorder owing to the emergence of symptoms during mid to late stages of life, recent evidence suggests that neural defects can occur long before clinical

presentation. However, the precise nature of these defects remains poorly understood. To address this problem, we are using a SOD1 G93R zebrafish model of ALS. This model is advantageous as it harbours a genetically encoded stress reporter (HSP70:DsRed), allowing the study of neuronal defects at presymptomatic stages of the disease.

Using in vivo patch clamping in combination with imaging approaches we have examined the electrical activity of stressed neurons in the spinal cord of presymptomatic zebrafish. In agreement with previous observations, we find that stress is first observed in the inhibitory interneuron population during early stages of life (from around 2 days post fertilisation). Analysis of the physiological properties of these neurons reveals an increase in input resistance, a decrease in capacitance and an uncontrolled firing phenotype. These effects are accompanied by a marked reduction in inhibitory postsynaptic currents within the spinal network. Subsequent morphological analysis of stressed inhibitory interneurons also reveals defects in axonal growth. Our findings point to an early and very specific defect in the growth and function of inhibitory neurons during early stages of the disease. We posit that, over time, these changes may exacerbate motor neuron stress and accelerate progression to symptomatic stages of the disease.

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Poster number: P-M104
Theme: Neurodegenerative disorders & ageing

Activity, appetitive trace conditioning and novel object recognition: A longitudinal study of middle aged male rats

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Trace conditioning (TC) procedures test the ability to associate events across a trace interval, thus providing a behavioural assay for working memory impairment. Localised actions at mPFC dopamine (Pezze et al., 2015, Psychopharmacology, 232:2669-2680) and muscarinic receptors (Pezze et al., under revision) were demonstrated in appetitive TC. It has yet to be established whether appetitive TC is impaired in older rats. We therefore compared appetitive TC in two matched cohorts of male Wistar Han rats (N=24/cohort) at 2 and 12 months of age. Rats were conditioned on two consecutive days at 2 versus 10s trace intervals, at the same 6 week timepoints, up to 8 and 18 months of age. Nosepoking during noise (CS) presentations was used to track age-related decline in the ability to condition with food (US) over a trace interval. We compared responding in the inter-trial-interval (ITI) and when the US was delivered to distinguish non-specific motor and motivational effects of ageing. Within the longer (10s) trace interval, we also examined age-related changes in the distribution of responding which may reflect changes in timing ability.

Older rats showed reduced improvement from one day to the next, at the early timepoint measures of CS responding at the 2s trace interval (Figure 1A). When the cohorts were tested longitudinally up to 8 and 18 months of age (late adulthood through middle age, prior to likely neuropathological changes), older rats conditioned over the 2s trace (shown as increased CS responding). In contrast, levels of ITI responding dropped and US responding was maintained in the older cohort. At later timepoints, responding within the 10s trace progressively distributed towards the end of the trace, in the younger but not the older rats (Figure 1B). This suggests that only younger rats learned to time their anticipatory responding. Novel object recognition (NOR) tests were used to provide some positive control and there was initially some NOR impairment at a 24hr retention interval (Figure 1C). As the rats aged, sample exploration declined but the NOR discriminative responding recovered. Finally, neurotransmitter and metabolite levels in striatum and mPFC were determined by HPLC-ED. 5HIAA/5-HT was reduced at 18.5 months in dorsal striatum.

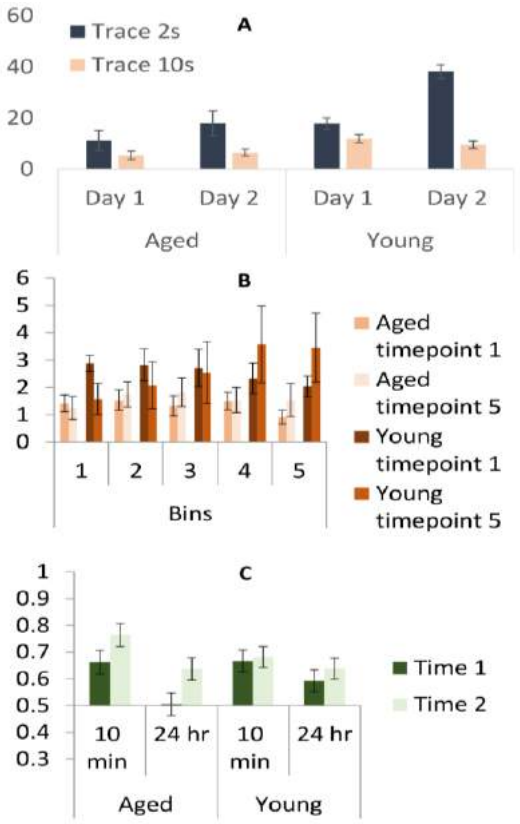

Figure 1. **(A)** Mean nose-pokes during the CS on each of two days at 12 vs 2 months. Darker shade denotes rats conditioned at the 2s trace interval and lighter shade denotes rats conditioned at the 10s trace interval. **(B)** Mean nose-pokes are shown as a function of the five 2s bins of the 10s trace interval for aged (lighter shades) versus adult rats (darker shades) and timepoint 1 (12 vs 2 months) versus timepoint 5 (18 vs 8 months). **(C)** Discrimination ratio scores at each of the two NOR test timepoints. A ratio of 0.5 indicates no discrimination; scores above 0.5 indicates a preference for the novel object. Tests at timepoint 1 (dark grey bars) were conducted at 14 vs 3 months. Tests at timepoint 2 (light grey bars) were conducted at 20 vs 9 months.

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Poster number: P-M105
Theme: Neurodegenerative disorders & ageing

Microglia in a protein misfolding environment have multiple complex responses which may determine susceptibility or resilience to neurodegeneration

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In many chronic neurodegenerative diseases specific proteins misfold and aggregate. It is understood that over time these protein aggregates continue to accumulate and spread around the central nervous system and eventually overwhelm neurons which degenerate and die. The progressive neurodegeneration is restricted to specific neuronal populations which show clear accumulation of misfolded proteins, whilst neighbouring neurons remain unaffected. This is true of a range of neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease and the prion diseases. Understanding the mechanism(s) of

neurodegeneration is of obvious importance but an undervalued, and almost completely unstudied, question is how and why some neuronal populations are resilient to neurodegeneration. Discerning such enigmas might provide vital clues to develop therapeutic interventions which, rather than aiming to prevent mechanisms of neurodegeneration, could be targeted to upregulate pathways to enhance neuroprotection.

To examine this avenue of research, we have utilised a sensitive assay for detection of misfolded protein (RT-QuIC) in a murine model of prion disease. Misfolded prion protein was observed widespread throughout the brain, accumulating in all brain regions examined irrespective of neurodegeneration demonstrating active mechanisms of protein misfolding in all brain regions1. Neither time of exposure nor amount of misfolded protein determined regions of neurodegeneration. This shows that unaffected brain regions during disease in fact accumulate misfolded protein raising the question of what is facilitating neuroprotection in these regions. We examined the global gene expression differences between brain regions which are susceptible or resilient to neurodegeneration and demonstrate two distinct microglia responses in prion-infected brains: a novel homeostatic response in all regions and an innate immune response restricted to sites of neurodegeneration1. We conclude that protein misfolding events alone do not define targeting of neurodegeneration, which instead manifests only when misfolded prion protein accompanies a specific innate immune response.

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Poster number: P-M106
Theme: Neurodegenerative disorders & ageing

Manipulation of amyloid precursor protein processing impacts brain bioenergetics and glucose metabolism

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The amyloid precursor protein (APP) and one of its terminal cleavage products, amyloid beta (Aβ) are proposed to play a central role in the pathogenesis of Alzheimer's disease (AD). These proteins have also been shown to co-localise within mitochondria with Aβ directly inhibiting the electron transport chain. Whilst these interactions with mitochondria have been noted, the impact of manipulating APP processing via the distinct α- and β-secretase pathways on cellular metabolism and bioenergetics has yet to be elucidated. We utilised the human SH-SY5Y neuronal cell line stably overexpressing BACE1 and cortical slices from mice bearing inducible overexpression of APP harbouring the Swedish and Indiana mutations, favouring Aβ production. Protein expression and enzyme activity were determined via western blotting and enzyme-linked immunosorbance assays (ELISA). A Seahorse extracellular flux analyser and radio-labelled substrate assays were used to determine cellular bioenergetics in real-time. All data are expressed as mean ± standard error of the mean and statistical significance determined by Student's t-test. Manipulation of APP cleavage resulted in alterations of 2-deoxyglucose uptake into cells. Chronic elevation in BACE1 resulted in impaired functioning of a key fuel-partitioning enzyme, pyruvate dehydrogenase (PDH, activity reduced to 69%). This reduced substrate delivery to the mitochondria and increased reliance upon aerobic glycolysis for ATP generation (oxygen consumption rate (OCR) reduced to 65% and extracellular acidification rate (ECAR) increased to 165%). Thus BACE1 overexpression impairs neuronal glucose oxidation resulting in an increased reliance upon aerobic glycolysis for ATP generation. Acute cortical overexpression of APP favouring amyloidogenic processing resulted in a significant reduction in PDH protein expression (reduced to 62%) and activity of key tricarboxylic acid cycle enzymes, isocitrate dehydrogenase and alpha-ketoglutarate dehydrogenase (reduced to 62% and 882% respectively). Therefore, manipulation of APP processing towards Aβ production in cells and tissue significantly impacts cellular metabolic pathways at the level of glucose uptake, substrate entry to the mitochondria and the TCA cycle.

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Poster number: P-M107
Theme: Neurodegenerative disorders & ageing

Imitative compatibility effects as evidence of motor resonance in Parkinson's disease

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Observation of biological movement influences the observer's own movements. This motor resonance can be seen in visuomotor priming, whereby movement is influenced by the compatibility between the intended and observed actions. These effects are underpinned by the action observation network, which includes cortical and subcortical motor areas. Movement disorders such as Parkinson's disease (PD) might be expected to impact on motor resonance; however, previous studies of visuomotor priming in PD have not differentiated imitative compatibility effects (specific to human movement) from general stimulus-response compatibility effects.

We tested visuomotor priming of hand movements in 23 participants with mild to moderate PD (63.5 ± 6.5 years; Hoehn & Yahr stage 2.0 ± .71) and 24 healthy older adults (68.3 ± 5.4 years), pitting imitative compatibility against general stimulus-response compatibility using a rotated image of a human hand compared with a non-biological shape (see Figure). Participants made a key press in response to a go-signal, following the presentation of a task-irrelevant compatible or incompatible moving finger or rectangle.

Imitative compatibility effects were found specifically for the human finger, and effects did not differ between groups, indicating intact motor resonance in the PD group. By controlling for general stimulus-response compatibility effects, we provide the first unambiguous evidence of imitative priming in both PD and healthy ageing. However, interference from observing incompatible movements correlated with disease severity (UPDRS motor examination), suggesting that imitative control may be affected in PD as the disease progresses.

These findings have implications for the development of therapies to facilitate movement based on action observation. Moreover, our results are relevant to the understanding of social cognitive deficits in PD, which have been linked to alterations in action representation.

Reference:

Gowen, E., Bolton, E., & Poliakoff, E. (2016). Believe it or not: Moving non-biological stimuli believed to have human origin can be represented as human movement. Cognition, 146, 431-438.

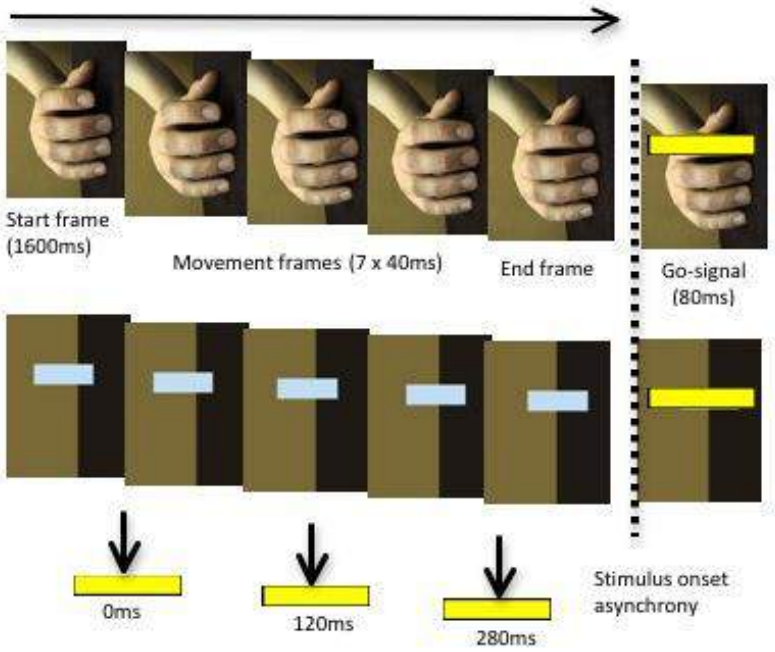

Figure (adapted from Gowen et al., 2016). Visuomotor priming task: Participants observed a moving human hand or non-biological shape and responded to a go-signal (yellow 'flash') with a left-handed key press. A rightward movement of the finger represents a downward action, so faster responses following observation of rightward movements indicate imitative compatibility with the finger press. Conversely, a leftward movement of the shape is orthogonally and spatially compatible with the left-handed press response; faster responses following leftward movements therefore indicate general stimulus-response effects.

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Poster number: P-M108
Theme: Neurodegenerative disorders & ageing

Rescuing synaptic activity in mice with prion disease

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It has been suggested that S-nitrosylation is involved in the pathogenesis of various neurodegenerative disorders including Parkinson's disease (PD), and Alzheimer's disease (AD). The neuroinflammation that characterize these pathologies is largely associated with an elevated production of nitric oxide (NO) leading to abnormal protein S-nitrosylation. Here we use a mouse model of neurodegeneration to investigate the role of nitric oxide mediated pathways at the synapse and its contribution to neuronal decline. We show that in prion-infected mice synaptic activity is dramatically decreased. Indeed the amplitude and frequency of miniature EPSCs are lowered together with potassium currents. However chronic injection of a NOS inhibitor L-NAME totally rescues presynaptic release probability / the number of functional synaptic sites and the density/conductance of postsynaptic receptors at individual synapses. We further show that the expression of synaptic proteins synapsin and complexin1/2 diminishes in prion-infected mice as the disease progresses. Future work will evaluate the effect of chronic L-NAME treatment on synaptic protein expression and nitrosylation status.

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Poster number: P-M109
Theme: Neurodegenerative disorders & ageing

Acyl-ghrelin regulates the methylation of key neurogenic and neuroprotective gene promoters

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Adult hippocampal neurogenesis (AHN) is the process of generating new, fully functional neurones from pools of neural stem cells in the sub-granular zone (SGZ) of the dentate gyrus (DG). AHN occurs throughout life and is important for pattern separation memory. It is regulated by a plethora of physiological and environmental factors. Recent studies suggest that epigenetics, which involves the heritable processes of regulating gene expression,without altering the DNA sequence, as an important modulator of AHN. Examples include DNA methylation, chromatin re-modelling and histone modifications. One epigenetic modulator of AHN is the immediate early gene, Gadd45b. Its transcription is sensitive to many environmental stimuli and its expression in mature DG neurones induces de-methylation of neurogenic gene-promoters, such as fibroblast growth factor (Fgf1b) and brain-derived neurotrophic factor (Bdnf).

In this study, we have studied whether the stomach hormone, acyl-ghrelin (AG), which is known to promote AHN, regulates epigenetic marks on neurogenic gene promoters.

First, AG treatment (i.v 48ug/day for 7-days) increased Gadd45b mRNA expression in the hippocampus of adult mice in a GHSR-dependent manner ($P<0.05$). GHSR-eGFP mice were used to confirm Gadd45b/GHSR co-expression in the DG. Next, to determine whether AG was having a direct effect, we treated SN4741 neurones in-vitro with AG (1uM) for 4h and 24h. Subsequently, extracted gDNA was used for methylated/hydroxy-methylated DNA immuno-precipitation assays (MeDIP/hMeDIP), to determine the methylation status of gene promoters for BDNF IX, BDNF IV, FGF-1b, FGF-1g, FGF-2 and Oct-4. AG-treatment significantly reduced methylation (5-mc) and hydroxymethylation (5-hmc) of the FGF-1b promoter after 4h and 24h ($P<0.05$). No significant changes were seen in the promoter regions of FGF-1g, FGF-2, BDNF IX, BDNF IV and Oct-4. These data are consistent with AG acting directly on neurones to de-methylate the promoter region of an essential neurogenic gene. Further experiments are now warranted to determine the role of AG, which is both neurogenic and neuroprotective, in wider epigenetic regulation of neurone function.

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Poster number: P-M110
Theme: Neurodegenerative disorders & ageing

ER shaping proteins are required for ER and mitochondrial network organization in motor neurons

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Hereditary spastic paraplegias (HSPs) are a group of inherited neurodegenerative disorders characterized by degeneration of the longest motor neurons in the corticospinal tract, leading to muscle weakness and spasticity of the lower limbs. Pathogenic variants in genes encoding proteins that shape the endoplasmic reticulum (ER) network within axons are a leading cause of HSP. Despite this, the mechanisms by which loss of ER-shaping proteins lead to motor neuron degeneration in HSP remain poorly understood.

To begin to address this, we have generated a novel in vivo model of HSP in Drosophila melanogaster caused by the targeted knockdown of the ER-shaping protein Arl6IP1, the homolog of which has recently been shown to cause HSP. Arl6IP1 RNAi flies display progressive locomotor deficits without a marked reduction in lifespan, recapitulating key features of HSP in human patients. Loss of Arl6IP1 leads to a striking disruption to the ER network within motor neurons that is accompanied by a decrease in contact points between the ER and mitochondria and a disruption to the mitochondrial network in a length-dependent manner. Moreover, we find that genetically increasing mitochondrial division, by overexpressing dynamin related protein 1, restores the mitochondrial network within the distal ends of the longest motor neurons and rescues locomotor defects in 2 independent models of HSP.

Taken together, these results propose a role for ER-shaping proteins in mitochondrial network organization and suggests that and suggest that impaired mitochondrial organization may be a common mechanism underpinning some forms of HSP.

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Poster number: P-M111
Theme: Neurodegenerative disorders & ageing

Vascular endothelial growth factor receptors in dementia

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Introduction: Brain ischaemia is the defining pathological process in vascular dementia (VaD); however, cerebral blood flow is also reduced in Alzheimer's disease (AD) and there is evidence that the hypoperfusion contributes to tissue damage. Vascular endothelial growth factor-A (VEGF) is a pro-angiogenic factor expressed in response to tissue hypoxia. VEGF receptor 2 (VEGFR2) mediates the actions of VEGF on endothelial cells leading to the formation of blood vessels. VEGFR1 has limited kinase activity and its soluble form (sVEGFR1) acts as a negative regulator of VEGF. We previously reported that increased VEGF protein in AD was not associated with an increase in microvessel density1. Aβ42 was shown to bind to VEGFR2 and block signalling in vitro providing a possible mechanism for reduced angiogenesis2; however, there are no studies of VEGFR1 or VEGFR2 in AD brain. We have investigated the expression of these receptor proteins in parietal cortex in AD and controls, and related this to VEGF, microvessel density and Aβ levels.

Methods: Samples of medial parietal cortex were dissected from 49 AD, 19 VaD and 37 control brains from the South West Dementia Brain Bank. Total VEGFR1 was measured by dot blot. Total VEGFR2 and von Willebrand factor (VWF, a marker of microvessel density) were measured by ELISA. VEGF, Aβ40 and Aβ42 had previously been measured in parietal cortex from the same brains.

Results: VEGFR1 was lower in AD than controls but VEGFR2 was similar in the two groups, as was VWF level, in agreement with previous data1. VEGFR2 level positively correlated with both VEGF and VWF. It also correlated positively with soluble Aβ40 but not Aβ42.

Conclusion: Elevated VEGF fails to increase microvessel density in AD despite normal VEGFR2 level and a reduction in VEGFR1 binding sites. This suggests that VEGFR2 signalling is defective in AD. Further research is needed to elucidate the underlying mechanism.

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Poster number: P-M112
Theme: Neurodegenerative disorders & ageing

Towards the therapy of Alzheimer's disease via the inhibition of a phospholipase A2 isoform using peptides able to cross the blood-brain barrier

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Alzheimer's disease (AD) is one of the main causes of dementia and its treatment is a real challenge. Phospholipase A2 (PLA2) signaling pathway was recently revealed to be involved in this pathology [1]; its inhibition has already been shown to protect neurons against apoptosis induced by amyloid beta (Aβ) [2]. Aiming to preclude the neurodegenerative effects of PLA2 by limiting its activation, we have identified a PLA2-targeted peptide (PL-P25) by phage display. PL-P25 is able to prevent the PLA2 binding to cell membrane phospholipids and restores its activity in the range of controls. In human astrocytes (1321N1) and mouse neurons (N18) induced by H2O2 and glutamate respectively, known as PLA2 activators, a lower release of arachidonic acid levels was observed following the incubation with PL-P25.

Furthermore, the treatment of brain diseases is complicated by the presence of the blood-brain barrier (BBB), protecting against xenobiotics and limiting the access of most molecules, including potential therapeutic agents. Non-invasive crossing strategies are thus indispensable to accede to the central nervous system (CNS) without BBB disruption. Because of its involvement in LDL transcytosis [3], LDL receptor (LDLR) turns out to be an attractive shuttling strategy for drug delivery. Following the LDLR-targeted phage display, the peptide LR-P2 was identified. This one colocalizes with LDLR on mouse brain slices and human brain endothelial cells (ACBRI376) and is endocytosed via a caveolae-mediated non-degradation pathway, whereas the lysosome degradation is bypassed. Recently, LR-P2 was covalently coupled to Ultrasmall Superparamagnetic Particles of Iron Oxide (USPIO-LRP2) and injected to healthy NMRI mice to evaluate the BBB crossing by Magnetic Resonance Imaging (MRI) and histology. USPIO-LRP2 was found within brain parenchyma, around the 3rd ventricle and brain capillaries, supporting the potential of LR-P2 to operate as a delivery agent of various pharmaceutical moieties, including our therapeutic peptide described above.

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Poster number: P-M113
Theme: Neurodegenerative disorders & ageing

INCREASED EXPRESSION OF IL-16 IN THE BRAIN LESION OF EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS MODEL

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Multiple Sclerosis (MS) is a demyelinating disease of the CNS, whose pathophysiology involves both inflammatory and neurodegenerative components. CD4+ T cells are one of the key mediators of disease initiation and progression; however CD4 is also the receptor for the pro-inflammatory cytokine, interleukin-16 (IL-16). IL-16 has been proposed to play a role in several autoimmune diseases, but the exact role of IL-16 in the CNS during MS initiation and progression remains unclear. Therefore, the aim of this study was to examine the expression and distribution of IL-16 in CNS tissue and investigate whether expression levels correlate with neuroinflammation in experimental autoimmune encephalomyelitis (EAE), a murine model of MS.

EAE was induced in 6 week old C57BL/6J female mice by immunisation with MOG35-55 peptide and adjuvants. Tissue was harvested at onset (day 11), peak (day 16) and resolution (day 26), and immunofluorescence staining carried out to determine CD45, CD4 and IL-16 expression and localisation in the brain of both control and EAE mice. In addition, co-localisation of IL-16 with CNS and immune cell subtypes was performed using a Mesolens microscope (McConnell et al., 2016), which allows subcellular detail to be obtained from wide-field epi-fluorescence images.

Expression of IL-16 and CD4 was observed primarily within the lesions of cerebellum and hippocampus of the EAE brain, whereas little expression was observed in control brains. IL-16 expression was highest at onset with 76 ±2.8% of cells (n=3) within these lesions expressing IL-16. This was reduced to 48±2.4% (n=3) at peak and 16 ±1.3% at resolution (n=3). Co-localization studies revealed that IL-16 was expressed primarily by infiltrating immune cells but not by neurons or astrocytes. Co-localization of IL-16 with immune cells in brain lesions of EAE mice suggests that infiltrating immune cells are the primary source of IL-16. Further investigation is required if IL-16 is pro-inflammatory or anti-inflammatory in the CNS during EAE.

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Poster number: P-M114
Theme: Neurodegenerative disorders & ageing

A Comprehensive "Disease-in-a-Dish" Approach to Parkinson's Disease

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Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide, affecting 3% of individuals >75 years of age. The disease is relentless and incurable, and has a heavy economic burden. Given the ageing populations of most high-income countries, the need to understand the causes of PD and develop new treatments is overwhelming.

PD genetics has been remarkably informative for early-onset forms of PD, leading to a widely accepted idea that it is a disease of mitochondrial dysfunction. By contrast, genetics has been less fruitful for more-common late-onset forms of PD. A number of potential pathological mechanisms have been proposed, including lysosomal perturbation, defects in protein and organelle clearance (i.e. impairments in the ubiquitin-proteasome system and/or autophagy), mitochondrial dysfunction, and deregulated cell signalling pathways (in particular, down-regulation of canonical Wnt signalling). However, there is little consensus; animal models have largely disappointed, and much of the in vitro data has relied on over-expression. The first events in PD aetiology – the deregulated processes that lead to α-synuclein accumulation and neurodegeneration – remain a mystery.

It is clear that alternative experimental models are required to unlock the potential of PD genetics. Thus, we are using Cas9/CRISPr-mediated genome editing to develop state-of-the-art human cell lines containing PD-causing mutations, starting with pathogenic LRRK2 mutations. The cell lines are isogenic, so they can be compared directly against each other, allowing common effects of mutation to be seen. Effects of mutation that are shared by most or all PD-causing mutations are likely to be central to the pathological process. As powerful controls we will also make cell lines containing protective mutations (e.g. LRRK2 R1398H). The cell lines will be studied using a combination of unbiased (e.g. proteomics, transcriptomics) and hypothesis-driven approaches (e.g. assays of lysosome function). We are confident that our study will yield new and important data about the aetiology of late-onset PD, and could lead to novel therapeutic strategies.

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Poster number: P-M115
Theme: Neurodegenerative disorders & ageing

Hyperglycaemia reduces mitochondrial motility and size in mature hippocampal cells

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Hyperglycaemia contributes to both the risk of developing neurodegenerative disease and to alterations in the function and dynamics of mitochondria. It has been shown previously that elevated glucose decreased axonal mitochondrial motility (Pekkurnaz et al. 2014). Complex and overlapping mitochondrial morphologies make analysis of mitochondrial dynamics challenging however; particularly beyond linear neuronal processes. We have developed image analysis techniques that enable the discrimination of individual mitochondria within optically-crowded environments (Chalmers et al. 2015) and can track mitochondria to sub-pixel resolution (Chalmers et al. 2012). Primary hippocampal cell cultures at 7, 14 and 21 days in vitro (DIV) were co-loaded with the

mitochondrial membrane potential (ΔΨm)-sensitive fluorophore tetramethyl-rhodamine ethyl-ester (TMRE), plus the ΔΨm-independent Mitotracker-Green for 1 hr in media containing either 5.5 or 25 mM glucose prior to epifluorescence imaging. For cells maintained to 21 DIV, mitochondrial motility was decreased in the high glucose media (4.76 ± 1.53% of total mitochondrial area moved min-1, n=9, compared to 8.04 ± 1.54% in 5.5 mM glucose, n=11; p=0.012), however there was no difference in the younger cells (7 DIV: 8.03 ± 3.13% total mitochondrial area moved min-1 at 5.5 mM glucose, n=14, c.f. 6.45 ± 1.89% min-1 at 25 mM glucose, n=15; 14 DIV: 6.37 ± 1.56% total mitochondrial area moved min-1 at 5.5 mM glucose, n=15, c.f. 6.78 ± 2.4% min-1 at 25 mM glucose, n=10). A wide range of mitochondrial morphologies were observed in all cell preparations and glucose concentrations, however there was a marked shift towards more small, punctuate mitochondria at 25 mM glucose, compared to a majority of elongated mitochondria at 5.5 mM glucose. In summary, hyperglycaemia causes a decrease in mitochondrial motility and size in mature hippocampal cells in culture, potentially contributing to cellular vulnerability by altering the involvement of mitochondria in calcium buffering or interactions with structures such as the endoplasmic reticulum.

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Poster number: P-M116
Theme: Neurodegenerative disorders & ageing

Refining functional endpoints in preclinical drug discovery for Alzheimer's disease: A case study using the rTg4510 mouse model of tauopathy

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The choice of disease models and efficacy endpoints is central to Alzheimer's disease (AD) drug discovery. True alignment of these and clinical research remains challenging; illustrated by the inability of mouse models to recapitulate the human disease. Current models exhibit various degrees and patterns of pathological burden and diverse ranges of functional alterations. Given this, the pathological and functional endpoints used in AD drug discovery must be determined on a model-by-model basis, but following a similar experimental process. The present work sought to use the rTg4510 mouse model of tauopathy as a case study to define best practices for the selection and validation of cognitive and functional endpoints in preclinical AD drug discovery.

Male rTg4510 mice were first tested in a wide range of behavioural assays at an advanced pathological stage (12-15 months of age). In addition to extensive pathological tau burden and brain shrinkage, old rTg4510 mice displayed profound locomotor hyperactivity coupled with selective spatial reference and working memory deficits. Four behavioural assays were selected for further validation work, with the aim of investigating longitudinally (from 4 to 12 months) whether behavioural performance changed as a function of both the accumulation and suppression of tau burden. Progressive changes in behaviour and cognitive function were detected, where hyperactivity and rewarded T-maze alternation performance were found to most correlate with hippocampal and cortical tau burden and atrophy. Doxycycline administration from 4 months led to a 50% suppression of transgene expression; sufficient to arrest subsequent increases in tau burden and atrophy, and concomitantly prevented functional decline as measured by all 4 behavioural assays.

This work outlines a two-stage experimental process by which to characterize any mouse model of AD, and allow identification of model specific functional endpoints for future drug discovery efforts. It was vital to demonstrate robust relationships with the progression and experimental manipulation of tau pathology itself, increasing the likelihood that such functional endpoints have a construct validity that is likely to be of translational relevance.

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Poster number: P-M117
Theme: Learning & memory

Dynamic Information coding by hippocampal-prefrontal (CA1-PFC) neural ensembles during spatial working memory

Authors: Aleksander Domanski - *Physiology Pharmacology and Neuroscience University of Bristol*

Distributed brain regions communicate by temporally aligning their spike trains to form “neural ensembles” that encode and bind salient information. The network bases of ensemble formation and information processing are poorly understood. Here, we use tetrode recordings from rat dorsal CA1 and medial prefrontal cortex (mPFC) to reveal contributions of neural ensemble activation to information coding during an instrumental delayed non-match to position task.

Local and inter-area cell ensembles were detected from 50ms binned CA1 and mPFC unit firing rate co-fluctuations (293 CA1 / 319 mPFC units recorded from 6 adult Long-Evans rats) using a novel factor analysis method. Overall, 30% of CA1 and 11% of PFC units participated in ensembles. Ensemble activation patterns locked to task events (e.g. lever presses) offered superior information coding (discriminating left vs. right-lever trials, or sample vs. choice lever context) compared to individual neuron firing rates. Temporal profiles of neurons’ and ensembles’ spatial and contextual information content differed between brain areas: unsupervised pattern analysis revealed sequences of encoding that were either sharply tuned to lever presses (typically CA1 neurons), or evolved slowly to maintain information about elapsed or upcoming actions (typical in mPFC).

Compared to their constituent neurons, ensembles showed reduced orthogonality between spatial and contextual encoding, thereby acting to stabilise information content over time. Spatial (left/right) information was best encoded by hippocampal ensembles, whereas the most robust contextual (sample/choice) encoding was carried by PFC ensembles. During errors, sample encoding remained accurate, but degraded throughout the delay in mPFC, culminating in prediction of the wrong response. Ensembles incorporating both CA1 and mPFC neurons were additionally most informative during post-choice outcome.

These results shed light on mechanisms of information encoding by limbic-cortical networks, revealing the sequential contributions of inter-regional ensembles in spatial working memory. In particular, mPFC ensembles emerge as multiplexed encoding channels able to bind and stabilise specific task-relevant information carried by their individual constituent neurons.

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Poster number: P-M118
Theme: Learning & memory

The effects of glucocorticoids on offline hippocampal spatial information consolidation and hippocampal-amygdala interactions during rest

Authors: Alice Fodder, Stafford Lightman, *School of Clinical Sciences University of Bristol,* Matthew W Jones, *School of Physiology, Pharmacology and Neuroscience University of Bristol*

Glucocorticoid hormones (corticosterone in rodents) are released in circadian cycles and acutely in response stress. Corticosterone activates mineralocorticoid and glucocorticoid receptors throughout circuits underpinning memory processing, including the hippocampus (HPC), basolateral amygdala (BLA) and prefrontal cortex (PFC). However, the net consequences of circadian and acute glucocorticoids for sleep-dependent memory consolidation remain unclear. We therefore quantified the effects of systemic corticosterone on network activity in HPC, BLA and PFC using in vivo local field potential (LFP) and multiple single neuron recordings in behaving/sleeping adult rats.

Injection of 3mgkg-1 i.p. corticosterone recapitulates systemic levels reached following stress. In an object-location test of rats’ ability to discriminate between objects in familiar and novel locations, corticosterone injected immediately after exploration of 2 identical objects impaired memory for object location 6h later: rats showed significant discrimination following saline injection ($p<0.05$, $t=3.56$ paired t-test), but not following corticosterone ($p>0.85$, $t=0.19$; n=6 Lister-Hooded). This indicates impairment of offline memory consolidation by corticosterone. However, in a parallel set of experiments recording network activity in CA1 and CA3 of HPC (n=4 Lister-Hooded), 3mgkg-1 i.p. corticosterone did not significantly impact mean firing rates of pyramidal cells (25 cells in CA3; 124 in CA1) or 120-250 Hz hippocampal ripple properties during rest/sleep, suggesting extra-HPC mechanisms. We next characterised corticosterone’s effects on interactions between CA1, BLA and PFC using simultaneous LFP recordings (n=6 Wistar). Here we found a marked enhancement in coupling between CA1 ripples and 60-100Hz gamma oscillations in BLA ($p<0.05$ Wilcoxon) following 3mgkg-1 corticosterone.

These data highlight a novel network mechanism through which stress may impact memory consolidation during rest/sleep by inducing aberrant coupling between the hippocampus and amygdala. We are currently quantifying how this may culminate in impaired spatial mapping via a decreased stability of hippocampal place cell codes.

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Poster number: P-M119
Theme: Learning & memory

Gluing memories via oscillations: Theta phase synchrony drives associative memory formation in humans

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The objective of our experiments was to investigate the causal role of neural synchrony between visual and auditory processing regions on associative memory formation for multisensory events.

Multisensory episodic memories rely on successfully binding elements that are processed in separate, specialised brain regions. The formation of episodic memories is thought to rely on the synchronization between distant brain regions in the theta frequency band. However, causal evidence for this idea from humans is missing. To provide such evidence we developed a novel multisensory memory paradigm where participants encode sound-movie associations.

Modulating the luminance and amplitude of the videos and sounds independently allowed us to control the degree of phase synchrony between the auditory and visual cortex. We then show in two experiments that memory for the sound-movie associations differs drastically depending on the degree of inter-sensory phase synchrony.

In the first experiment, in the encoding phase, all participants were shown short (3-second) videos that were luminance modified with a 4 Hz sine wave, with an accompanying audio clip that had been amplitude modulated with a 4 Hz sine wave. The phase offset (i.e., synchrony) between the audio clip and the video was 0, 90, 180, or 270 degrees. In a second experiment, the videos and sounds were modulated at 4 Hz, 1.7 Hz (delta), and 10.5 Hz (alpha). On each trial, participants rated how well the audio clip suited the contents of the video clip. Each of six blocks contained 16 audio-video pairings (four at each phase angle), and was followed by a brief distractor task and an associative recognition test.

Associations were better remembered in the synchronous compared to the asynchronous condition. This effect was specific to theta (i.e. 4Hz) and did not occur in a faster (10.5 Hz) or slower frequency (1.7 Hz). These findings suggest that episodic memory formation in humans relies on a theta specific synchronization mechanism.

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Poster number: P-M120
Theme: Learning & memory

Hippocampal synchronisation and neocortical desynchronisation co-occur during episodic memory formation

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The link between episodic memory formation and neural oscillatory activity is well-documented. However, the literature is conflicting with both oscillatory synchronisation and desynchronisation purported to facilitate encoding. In a step to resolve this contradiction, a recent opinion paper proposed that both are necessary for memory formation (Hanslmayr, Staresina & Bowman, Trends in Neurosciences, 2016). Specifically, desynchronised neocortical activity facilitates information processing of an ongoing event while synchronised theta and gamma oscillations within the hippocampus serve to bind this information into a coherent episode. Here, we tested this proposed interaction between the hippocampus and neocortex during memory formation. Epileptic patients with hippocampal depth electrodes learnt video-word pairs then were later cued with the word and asked to recall the associated video. Preliminary analysis revealed neocortical low frequency power decreases (3-20Hz), hippocampal theta and gamma power increases and greater hippocampal theta-gamma phase-amplitude coupling for later remembered items relative to

later forgotten items. Critically, there was a significant negative correlation between hippocampal theta/gamma power and neocortical low-frequency power such that as hippocampal synchronisation increases, neocortical desynchronisation increases. This finding supports the theory that hippocampal synchrony and neocortical desynchrony co-occur during episodic memory formation.

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Poster number: P-M121
Theme: Learning & memory

Hippocampal synchronisation and neocortical desynchronisation co-occur during episodic memory formation

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The link between episodic memory formation and neural oscillatory activity is well-documented. However, the literature is conflicting with both oscillatory synchronisation and desynchronisation purported to facilitate encoding. In a step to resolve this contradiction, a recent opinion paper proposed that both are necessary for memory formation (Hanslmayr, Staresina & Bowman, Trends in Neurosciences, 2016). Specifically, desynchronised neocortical activity facilitates information processing of an ongoing event while synchronised theta and gamma oscillations within the hippocampus serve to bind this information into a coherent episode. Here, we tested this proposed interaction between the hippocampus and neocortex during memory formation. Epileptic patients with hippocampal depth electrodes learnt video-word pairs then were later cued with the word and asked to recall the associated video. Preliminary analysis revealed neocortical low frequency power decreases (3-20Hz), hippocampal theta and gamma power increases and greater hippocampal theta-gamma phase-amplitude coupling for later remembered items relative to later forgotten items. Critically, there was a significant negative correlation between hippocampal theta/gamma power and neocortical low-frequency power such that as hippocampal synchronisation increases, neocortical desynchronisation increases. This finding supports the theory that hippocampal synchrony and neocortical desynchrony co-occur during episodic memory formation.

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Poster number: P-M122
Theme: Learning & memory

Retrieval as a fast route for consolidation: evidence from decontextualizaton and semanticization of memory representations

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The fact that retrieval can act as a powerful memory enhancer has been well established in the literature. However, the neurocognitive mechanisms underlying such enhancement are still unknown. One possibility is that retrieval solidifies memories through online reactivation mechanisms similar to those involved in offline memory consolidation (e.g. during sleep). If retrieval does indeed depend on neural memory reactivation, one could expect that new episodic memories, initially rich in contextual detail, to become gradually decontextualized as they undergo retrieval, and to transform into gist-like semantic representations. To test these decontextualization and semanticization hypotheses, we conducted a pattern fMRI study. Participants encoded scene-object pairs, with objects belonging to a number of different semantic categories. They then either retrieved or restudied the objects over two sessions, 48 hours apart. Using Representational Similarity Analysis, we traced the dynamic changes in item-specific and categorical activation patterns representing each memory in high order visual areas. Results show that across sessions, contextual information encoded at study (such as background colour) becomes lost across retrieval repetitions to a greater extent than across restudy ones. Moreover, retrieved (as opposed to restudied) objects become, neurally, less individualised, and more semanticized. Taken together, these findings support the hypothesis that retrieval can act as a fast route to memory consolidation.

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Poster number: P-M123
Theme: Learning & memory

Boundary conditions on instrumental memory reconsolidation

Authors: Chaoran Cheng, Marc Exton-McGuinness, Jonathan Lee, *School of Psychology University of Birmingham*

Long-term Memory can integrate new information through a mechanism called reconsolidation. During reconsolidation, memory destabilises into a labile state, integrates new information and reconsolidates again. Instrumental memories, which associate a particular action with an outcome, have recently been shown also to undergo reconsolidation. Importantly, there appeared to be a requirement for memory updating in order to destabilise the instrumental memory. This was achieved originally by using a change in instrumental contingency from FR1 during training to VR20 at memory reactivation. Here, we studied further the capacity of instrumental memories to destabilise.

First, we tested the hypothesis that the different memories conditioned during training compete at reactivation, thereby influencing destabilisation. In particular, instrumental training also results in context-reward learning. Therefore, the contextual memory and instrumental memory might compete for destabilisation. If the strength of contextual memory is weakened, the instrumental memory may easier to destabilise. Adult male rats were trained for 10 days under an FR1 schedule of reinforcement. A post-training context extinction session rendered a subsequent VR5 reactivation session sufficient to destabilise the instrumental memory, as evidenced by an amnesic effect of pre-reactivation injection of MK-801. MK-801 prior to VR5 reactivation (i.e. without the context extinction) had no impact on instrumental performance. However, context extinction itself may not be necessary, as a simple day off with no behavioural session was also sufficient to render a VR5 reactivation session effective. In order to test whether a day off induces forgetting of the contextual memory, we injected memantine on the day off to prevent forgetting. However, this facilitated instrumental memory destabilisation, suggesting that the day off and context extinction facilitate memory destabilisation via different mechanisms. In summary, there are emerging behavioural strategies to optimise the destabilisation of instrumental memories.

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Poster number: P-M124
Theme: Learning & memory

Lesion based dissociations in instrumental contingency learning: contributions of the ventromedial prefrontal cortex vs. superior motor regions

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Adaptive goal-directed behaviour relies on detecting the causal association between actions and their outcomes. This process of contingency learning is of great interest in neuropsychiatric conditions where goal-directed behaviour is impaired, but the specific neural correlates and psychological mechanisms are poorly understood. Previous work in animals and correlational fMRI studies in healthy people has implicated distinct fronto-striatal circuitry underpinning aspects of contingency learning, in particular dissociating the contribution of medial prefrontal and more superior cortical regions. In the current study, we aimed to explore the causal contributions of ventromedial prefrontal cortex (VMPFC) vs. superior motor regions to contingency learning in patients with stable lesions in those areas (N = 7 VMPFC and 7 superior lesion patients). We employ a novel instrumental contingency learning task that allowed us to measure responses to varying levels of outcome contingency relationships (probability that the action is followed by a reward: P(O|A)) and also under conditions of degraded contingency (probability the reward

occurs in the absence of an action: P(O|-A)). Additionally, we asked participants to rate the action-outcome contingencies. Therefore, we measured both behavioural adaptation to contingency changes, and also the perceived causal relationship. We found a dissociation in performance in the lesion groups: VMPFC patients were impaired in their response rates and contingency judgements under varying values of P(O|A) and performance in the superior lesion was relatively intact ; whereas under the degraded conditions P(O|-A), the superior lesion patients showed impaired contingency judgements, and the VMPFC group was unimpaired. Our results suggest that the VMPFC is critical for encoding the probability that an action is followed by an outcome, whereas encoding non-contingent information involves more superior/dorsal circuitry. Our results are consistent with previous fMRI investigations and animal literature, and extend these to a human lesion model. Extensions to the current results are to

incorporate additional patients and perform voxel-wise neuroimaging analyses to relate performance to patients' lesion size and site.

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Poster number: P-M125
Theme: Learning & memory

Synthetic glucocorticoid treatment causes dysregulated activation dynamics of glucocorticoid receptors in brain and pituitary

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Endogenous glucocorticoids (GCs) including cortisol and corticosterone exhibit a characteristic pulsatile secretory pattern. This pulsatile GC pattern induces a functional output in individual target cells, acting via the intracellular glucocorticoid receptor (GR), which is activated in distinct pulses causing a 'gene pulsing' effect. However, the effects of the more potent, long acting, synthetic GCs (sGCs) on GR dynamics is less well understood. We have therefore assessed the duration of GR activation in the mouse pituitary corticotroph cell line AtT20, and in the pituitary and brain of rats after treatment with the sGCs dexamethasone (Dex) and methyl-prednisolone (MPL) in comparison to the endogenous ligand corticosterone. We report the expected transient 'pulsatile' GR activation when a pulse of corticosterone was applied to AtT20 cells, as well as in pituitary, prefrontal cortex, hippocampus, perirhinal cortex and amygdala of rats given a single subcutaneous corticosterone injection. In contrast to this, we found a prolonged GR activation profile of over 6 hours with MPL and over 12 hours with Dex in the AtT20 cell line and in rat pituitary. In the brain, prolonged GR activation was also seen, although this was of a shorter duration than in the pituitary. GR activation continued for over 3 hours with MPL, and over 6 hours with Dex. The prolonged duration of GR activation with the sGCs compared to corticosterone is most likely the combined result of their higher potencies, longer GR binding durations, and longer half lives in the circulation. The shorter duration of sGC induced GR activation in the brain compared to the peripherally has previously been described to occur as a result of the MDR p-glycoprotein efflux transporter, which actively shunts the sGCs from the brain. Despite this protective mechanism, higher doses of sGCs can access the brain and cause prolonged GR activation when compared to the endogenous ligand. As the ultradian GR activity rhythm in the brain has been shown to regulate gene expression, and maintain neuronal function, the prolonged GR activation associated with sGCs may induce the adverse behavioural, cognitive and affective state side-effects reported in patients treated with sGCs.

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Poster number: P-M126
Theme: Learning & memory

Hippocampal Subfield Volumes Predict Memory Consolidation in Older Adults

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Human memory performance is predicted by individual differences in hippocampal size - perhaps due to its involvement in processes involved in storing and organising information. Intracranial recordings in animals and humans suggest that synaptic plasticity within the cornu ammonis (CA)1 region of the hippocampus provides an anatomical basis for initial stages of consolidation. From there, the subiculum is proposed to play a role in generating firing patterns that support transfer of information from the hippocampus to neocortical and limbic regions, supporting later storage. Due to their functional involvement, we hypothesised that CA1 and subiculum volumes, measured using magnetic resonance imaging (MRI), predict episodic memory consolidation. 3T MRI scans were acquired using a CPMG-like in-house developed sequence (in-plane resolution = 0.34 x 0.34mm2) from 74 older adults (49-88 years). Volumes of hippocampal subfields CA1, CA2, CA3, dentate gyrus (DG) and subiculum were segmented manually in FSL, and normalised to total brain volume. Memory was assessed using the Hopkins Verbal Learning Task (HVLT-R) in which free recall is tested immediately and following a 20 minute delay. Consolidation was measured as the percentage of words retained at 20 minutes. In a stepwise linear regression CA1 ($R2=.191$, $p<.001$), but no other subfields or age, predicted consolidation. To overcome multicollinearity, bivariate correlations were also calculated revealing associations with CA1 ($r=.437$,

p<.001), DG (r=.335, p=.002) and subiculum (r=.349, p=.002). For immediate recall, a non-significant trend was observed with the DG (r=.220, p=.059), but no associations were found with other subfields. These results demonstrate that larger CA1 is the best predictor of consolidation success in a verbal memory task. CA1 and subiculum volumes may support consolidation selectively while DG may play a more global role in memory processes.

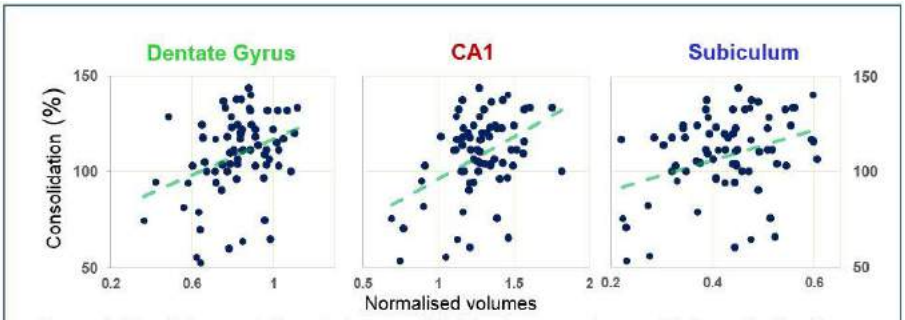

Figure 1. Bivariate correlations between subfield volumes and consolidation of episodic verbal memory revealed significant positive associations with the dentate gyrus (r=.355, p=.002), the CA1 (r=.437, p<.001) and the subiculum (r=.349, p=.002). These findings remain significant after correcting for multiple comparisons.

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Poster number: P-M127
Theme: Learning & memory

Sex Differences in Discriminating Between Cues Predicting Threat and Safety

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Post-traumatic stress disorder (PTSD) is more prevalent in women than men. PTSD is characterised by overgeneralisation of fear to innocuous stimuli and involves impaired inhibition of learned fear by cues that predict safety. While evidence indicates that learned fear inhibition through extinction differs in males and females, less is known about sex differences in fear discrimination and safety learning. Here we examined auditory fear discrimination in male and female rats. In Experiment 1A, rats underwent 1–3 days of discrimination training consisting of one tone predicting threat (CS+; presented with footshock) and another tone predicting safety (CS-; presented alone). Females, but not males, discriminated between the CS+ and CS- after one day of training. After 2–3 days of training, however, males discriminated whereas females generalised between the CS+ and CS-. In Experiment 1B, females showed enhanced anxiety-like behaviour and locomotor activity in the open field, although these results were unlikely to explain the sex differences in fear discrimination. In Experiment 2, we found no differences in shock sensitivity between males and females. In Experiment 3, males and females again discriminated and generalised, respectively, after three days of training. Moreover, fear generalisation in females resulted from impaired safety learning, as shown by a retardation test. Whereas subsequent fear conditioning to the previous CS- retarded learning in males, females showed no such retardation. These results suggest that, while females show fear discrimination with limited training, they show fear generalisation with extended training due to impaired safety learning.

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Poster number: P-M128
Theme: Learning & memory

The early life immune stimulation induces a sex differences in long-lasting modifications in cognitive behavior

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Background: Aging is one of many factors associated with an increased susceptibility to neurodegenerative disorders which can be related to early life inflammation. Early life immune stimulation, however, can be characterized by the increase in cytokines, oxidative stress as well as changing in microglia phenotypes from activated to priming during the age. Indeed the early neuroinflammation can profoundly affect brain function which can elicit behavioral impairments and cognitive deficits.

Objective: The aim of our study is to explore the sex differences and the possibilities to accelerate the cognitive decline associated with aging after a neonatal immune stimulation.

Methods: Male and females Wistar rats were treated on a postnatal day 14 with PBS or LPS, and then tested for learning & memory at 3 or 10 months of age, using novel object, Y-maze, and a spatial water maze task.
Results: Neonatally-infected rats exhibited memory impairments in the water maze, but only at 10 months. And no significant differences in novel object and Y-maze. Neonatally-infected rats also exhibited greater aging-induced increases in a number of microglia-activating in DG, CA1, and CA3, as well as an increase in Nitrite Oxide and lipid peroxidation but not TNFα within the hippocampus, but not in prefrontal cortex compared to controls.

Conclusion: Taken together, these data suggest that early-life infection leads to less successful cognitive aging, which may be linked to changes in microglial reactivity.

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Poster number: P-M129
Theme: Learning & memory

Effect of Melatonin on brain oxidative stress, senescence marker protein-30 and osteopontin in a rat model of vascular dementia

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Chronic cerebral hypoperfusion due to cerebrovascular disease is usually associated with loss of cognitive ability, including memory, language, attention and problem-solving, making it a serious medical, social and economic burden to society. The indoleamine melatonin, beside its critical role in the regulation of circadian rhythm, has antioxidant, anti-inflammatory and antiapoptotic properties. The aim of the present work was to investigate the effect of melatonin on oxidative stress, the anti-aging senescence marker protein-30 (SMP30) and the anti-apoptotic osteopontin (OPN) in a rat model of vascular dementia (VD).

Forty-eight male Sprague-Dawley rats (170-200 g BW) were randomly divided into four groups (n=12; each): 1. Control, 2. Rats exposed to VD by permanent bilateral occlusion of the common carotid arteries (BCCAO) leading to chronic cerebral hypoperfusion, 3. VD rats treated with melatonin (190 µg/100g BW; oral) for 28 consecutive days, starting the day after BCCAO, 4. VD rats treated with donepezil (3 mg/kg BW/day; i.p.). At the end of experiments, all rats were humanely killed, under terminal anaesthesia, by cervical dislocation. Expression of OPN was determined by immunohistochemistry, and SMP30 expression determined by western blot in the hippocampus. Hippocampal thiobarbituric acid reactive substances (TBARS) and total anti-oxidant capacity (TAC) were evaluated. Central levels of acetylcholine, norepinephrine and dopamine in the hippocampus were also measured. Significance ($P < 0.05$) was tested with ANOVA.

Rats exposed to BCCAO had significantly lower TAC and higher TBARs, compared to control. Additionally, BCCAO caused significantly lower expression of both OPN and SMP30. The central levels of acetylcholine, noradrenaline and dopamine were lower in VD rats as compared to control. Treatment of VD rats with melatonin significantly increased the expression of OPN and SMP30 as well as the central levels of acetylcholine in the hippocampus, as compared to untreated VD rats. Moreover, melatonin produced significant increase in TAC and decrease in TBARS.

It could, therefore, be concluded that, in a rat model of vascular dementia, melatonin ameliorates the brain oxidative stress, and produces a neuroprotective effects via upregulating SMP30 and OPN.

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Poster number: P-M130
Theme: Learning & memory

Investigating BDNF-dependent long range signalling from the synapse to the soma

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Neurons extend axons and dendrites to cover large areas. These extensions allow them to connect with other cells forming complex networks. Synaptic connections at distal axonal processes are far from the cell soma. A key question is how information transmitted from the distal axon is relayed to the soma? How this information is subsequently integrated and interpreted at the soma to modulate neuronal function may inform our understanding of neuronal network development, refinement and modulation. Structural changes need to be closely coupled to activity-dependent events in order to strengthen active synapses and abolish or dampen unused connections. The neurotrophin brain-derived neurotrophic factor (BDNF) provides an example of a highly regulated growth factor that triggers intracellular processes to initiate protein synthesis dependent and independent changes in cell function. BDNF signals through the tyrosine kinase receptor TrkB. TrkB activation by BDNF has been shown to modulate neuronal growth, arborisation, axonal branching and synaptic transmission. However, the precise intracellular mechanisms underlying the effects of BDNF on morphology are not well characterised. Specifically what are the long-range axonal signaling pathways activated, and what is their outcome on cellular function?
Using microfluidic compartmentalization, we have shown that distal axonal TrkB activation initiates immediate early gene expression and protein production in the somatodendritic compartment of hippocampal neurons. Our data suggest that this activation is independent of long-distance trafficking of the BDNF-TrkB complex itself. Current work addresses the underlying mechanisms of information relay along hippocampal axons, and their functional consequences.
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Poster number: P-M131
Theme: Learning & memory

Not just reinforcement learning: dopamine's role in retrieval of reinforcement

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Dopamine is thought to play a role in learning from rewards and punishments, but its role in other stages of memory (i.e. consolidation and retrieval) have been hard to differentiate. We used a within-subject, double-blinded, placebo-controlled paradigm to examine the effect of levodopa on retrieval during a reward and punishment task. 33 healthy older participants (18 male, mean age=71.8 years, SEM=1.31) learned on day 1 and were given drug/placebo 24 hours later, 1 hour prior to testing of retrieval. The reward/learning task (based on Pessiglione et al. (2006) presented i) a gain card pair where card A had an 80% chance of winning 20p, and 20% chance of nothing, and vice versa for card B, ii) a look pair where card C had an 80% chance of showing a 20p (but not winning or losing) and 20% chance of nothing, vice versa for card D; and iii) a loss pair, where card E had 20% chance of losing 20p and 80% chance of nothing, and vice versa for card F. Memory retrieval was tested immediately, 30 minutes and 24 hours after learning, the last on drug or placebo. For each memory test, cards were presented in all combinations without feedback. At 24 hours, participants avoided the 80% losing card significantly better on levodopa than on placebo. Medication state did not change behaviour on other cards. Overall accuracy was also unaffected. In contrast to the putative effects of dopamine during learning, higher levels of dopamine during retrieval results in avoidance of memories learned through punishment. Computational modelling will be used to provide possible mechanisms by which this might occur.

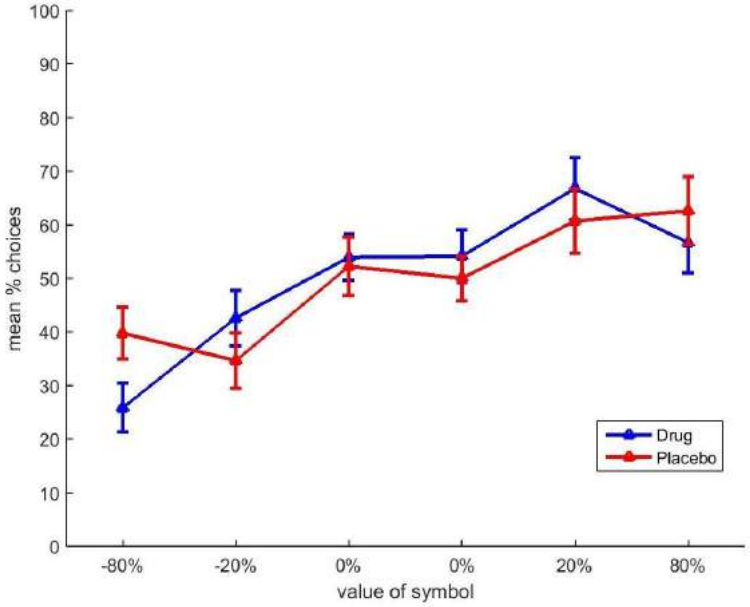

Figure 1 The mean percentage of choices of each card in the 24 hour novel pairs test, for drug and placebo conditions. The value of the symbol is the probability of the outcome, with negative values representing the loss cards, and positive the gain cards (i.e. -80% = 80% chance of loss). The two 0% symbols are the look pair. Participants chose the 80% loss card less when on Levodopa during the test.

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Poster number: P-M132
Theme: Learning & memory

Estrogens modulate excitatory synaptic transmission at hippocampal temporoammonic-CA1 synapses

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Estrogens, a class of steroid hormones, are primarily produced within the ovaries and influence reproductive function. Additionally, estrogen production is also found in the CNS and estrogen receptors (ERs) are located within many brain regions including the hippocampus (Mitra et al. 2003; Lephart et al. 2001). This non-traditional source of estrogen production highlights estrogen's potential to modulate cognitive functions. The ability of estrogens to modulate excitatory synaptic transmission have been investigated at hippocampal Schaffer Collateral (SC) –CA1 synapses (Warren et al, 1995). However, at the anatomically distinct Temporoammonic (TA) input to CA1 synapses, the effects of estrogens remain unclear (Smith et al. 2016). Here we have used standard extracellular recordings of field excitatory post-synaptic potentials (fEPSPs) to examine the effects of ER agonists on excitatory synaptic transmission at TA-CA1 synapses. Hippocampal slices (350μM) were prepared from juvenile male rats (P11-24) and perfused with oxygenated aCSF. In juvenile slices (P15), 17β-Estradiol (E2; 1μM; 15min) resulted in a biphasic response. Application of E2 caused initial depression of synaptic transmission (to 81 ± 12.7% of baseline; n=5; $p>0.05$) that was followed by a significant and persistent increase in synaptic transmission on washout (to 124 ± 3.6% of baseline; n=5; $p<0.001$). The non-selective nature of E2 and its ability to activate different ERs may provide an explanation for this biphasic response. These data indicate that E2 has the ability to bi-directionally modulate excitatory synaptic transmission at TA-CA1 synapses. Understanding the role of estrogen, and its receptors, at TA-CA1 synapses may be important as the TA pathway is believed to play a role in episodic memory (Remondes & Schuman 2004) and impairments in episodic memory is an early symptom of Alzheimer's Disease (AD) (Hodges 2000). Therefore, these initial findings are important for understanding estrogenic regulation of hippocampal excitatory synaptic function in CNS health and disease

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Poster number: P-M133
Theme: Learning & memory

Boundaries between contextual fear memory reconsolidation and extinction

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Retrieval of an associative memory can lead to two different phenomena depending on several factors, such as the duration of stimulus re-exposure. Brief stimulus re-exposure tends to trigger memory reconsolidation, whereas more extended re-exposure leads to memory extinction. Impairment of reconsolidation reduces memory expression, while disruption of extinction maintains expression. Interestingly, it has being observed that during the transition from reconsolidation to extinction of appetitive or aversive pavlovian explicit CS-US memory, there is period where amnesic agents have neither effect. These observations indicated the existence of a "null point" where neither reconsolidation nor extinction is being engaged. Here we investigated whether thisphenomenon extends to contextual fear memory. Adult male lister hooded rats were subjected to a Contextual Fear Conditioning (CFC) paradigm. During training, rats were placed in the chamber for 3 min, received 2 foot shocks (0.7 mA 1.5 sec), and after 1 min, returned to their home cages. Two days later, animals were re-exposed to the same context for 3, 5, 10, 20 or 30min. Immediately after re-exposure, the amnesic agent MK-801 was injected intraperitoneally (0.1 mg/kg). On the next day, animals were exposed again to the context, for 3 min, in order to test memory expression. The aversive response (freezing) was recorded during all sessions and used as memory index. We observed that MK-801 had a significant effect when administered after 3min or 30min reactivation sessions. However, it did not have any significant effect when injected after either 5, 10 or 20min sessions. Further analysis of larger cohorts of animals indicated that the lack of effect of MK-801 when injected after 5 or 10-min sessions are not likely a result of inter-individual differences (e.g. Low vs High freezing animals or reconsolidating vs extinguishing animals).In conclusion, the results show that in contextual fear memories there is a "null point" of 5-20-min re-exposure between the parameters that induce reconsolidation (3 min) and extinction (30 min), at which the memory is insensitive to any effect of i.p. MK-801. Therefore, extinction per se does not exert a boundary condition on memory reconsolidation.

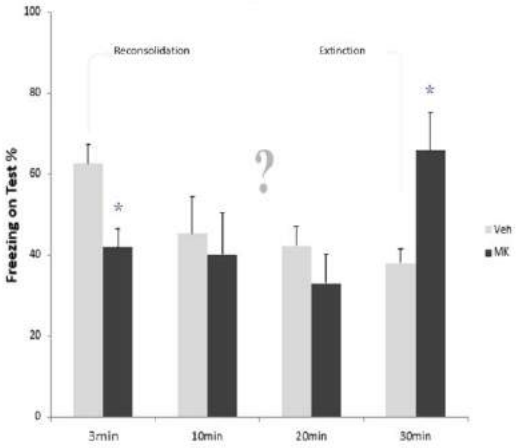

Figure 1A: CFC memory is insensitive to MK-801 between the parameters that induce reconsolidation (3min) and extinction (30min). *$p<0.05$. Independent *t*-test. $n=7$-11 per group.

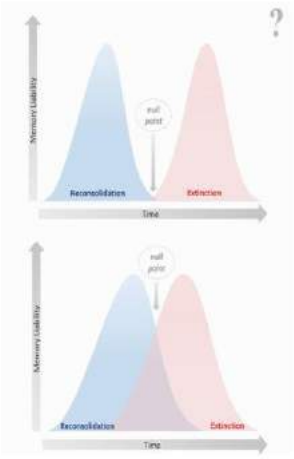

Figure 1B: The null point could result from a within-subjects process (top panel) or between-subjects differences (bottom-panel).

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Poster number: P-M134
Theme: Learning & memory

Disrupting reconsolidation of lever pressing memory reduces spontaneous drug-seeking for cocaine but not nicotine

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A key obstacle in the treatment of addictions is the high propensity for relapse. Recent research has suggested the propensity for relapse could be reduced by weakening the memories which underpin maladaptive drug-seeking. We recently demonstrated that weakly-trained instrumental lever pressing memory for cocaine could undergo reconsolidation, and here we aimed to replicate this finding in a well-trained setting using cocaine and nicotine reinforcement. Rats were trained for 10 d to self-administer intravenous infusions of drug by lever pressing; each drug delivery was paired with a 20-sec conditioned stimulus (CS) presentation. Following training rats were injected with the NMDAR antagonist MK-801 (or vehicle) 30 minutes prior to a short reactivation session in which the reward contingency was shifted to a variable ratio (VR5). Treatment with MK-801 reduced subsequent lever pressing the next day in cocaine-trained rats, when performance was tested in the absence of the CS, indicative of an impairment in the instrumental component of drug-seeking. Interestingly, this intervention also reduced rates of responding during a drug-primed test of cocaine seeking. However, performance was rescued when lever presses resulted in a 1sec CS presentation, suggesting memory for Pavlovian conditioned reinforcement remained intact. Notably MK-801 was without effect in the nicotine reinforced paradigm, possibly due to the generally weaker performance in nicotine-trained rats; however this may also reflect differences in neural mechanisms of cocaine and nicotine seeking. Implications for disrupting the reconsolidation of drug-reinforced appetitive memories are discussed.

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Poster number: P-M135
Theme: Learning & memory

The role of inhibitory alpha oscillations in human visual learning

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Learning is known to facilitate our ability to make perceptual judgements about our visual environment; that is extracting targets from cluttered scenes and discriminating similar objects. Previous functional MRI (fMRI) studies have shown differential activation patterns for these tasks; however fMRI does not allow us to differentiate between excitatory and inhibitory contributions to learning.

Here we use Electroencephalography (EEG) to measure inhibitory alpha range (8-12Hz) oscillations in the human brain during visual learning. We train participants to discriminate radial vs. concentric Glass patterns that a) are embedded in a noisy background (Signal-in-Noise task) or b) are highly similar (Fine Discrimination task). Our findings show reduced occipital alpha desynchronisation after training for low –rather than high– stimulus noise levels that show improved performance after training. Interestingly, occipital alpha desynchronisation is increased for noise levels that show stronger improvement with training. Further, for the Fine Discrimination task, we find that discrimination of highly similar features relates to increased occipital alpha desynchronisation.

Our results suggest that inhibitory alpha oscillations in the occipital cortex are modulated by visual learning. Occipital cortex involvement is reduced when processing trained features, as indicated by reduced alpha desynchronisation after training. In contrast, processing highly uncertain stimuli (high noise, high similarity) engages occipital cortex, as indicated by increased alpha desynchronisation. Our findings provide evidence that decreased inhibition mediates visual plasticity.

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Poster number: P-M136
Theme: Learning & memory

The role of NMDAR subunits in ventral hippocampal STP and LTP

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Synaptic plasticity is often studied in the CA1 area of dorsal hippocampal slices. Here, in response to high-frequency theta-burst stimulation (TBS), the Schaffer collaterals display two phases of potentiation readily induced through activation of NMDA receptors (NMDARs). The initial phase of potentiation, termed short-term potentiation (STP), declines in response to low frequency synaptic activation, leading to a permanently enhanced level of synaptic transmission, long-term potentiation (LTP). It has been recently shown that STP consists of two forms, termed STP1 and STP2 (Volianskis et al.,2013;2015). Induction of STP1 depends on activation of GluN2A/2B containing NMDARs, similar to LTP, which in the adult dorsal hippocampal slices is induced through GluN2A/2B containing triheteromeric NMDARs. In contrast, STP2 in the dorsal hippocampus is induced through GluN2B/2D containing NMDARs.

STP and LTP can also be induced in ventral hippocampal slices. However, the potentiation induced by TBS is smaller in the ventral hippocampus than in the dorsal. We report here that the NMDAR antagonist AP5 (3 µM and 30 µM) inhibited both STP and LTP induced by TBS in the CA1 region of ventral hippocampal slices from adult male Wistar rats. 0.1 µM NVP-AAM077 (NVP, a GluN2A selective antagonist), 1 µM Ro 25-6981 (Ro, a GluN2B selective antagonist) and 10 µM UBP145 (UBP, a GluN2D selective antagonist) were used to determine the identity of GluN2 subunits involved in synaptic potentiation. We show that NVP blocked both STP and LTP, whilst Ro had no effect on STP or LTP. UBP blocked STP and did not reduce LTP. Furthermore, we show that the GluN2A/2B preferring positive allosteric modulator UBP714 potentiates LTP in the ventral hippocampus. We conclude that in the ventral hippocampus GluN2A containing NMDARs are involved in the induction of LTP whereas induction of STP involves activation of GluN2D subunits.

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Poster number: P-M137
Theme: Learning & memory

Study of the in vivo dynamics of endogenous amines in Drosophila melanogaster Mushroom Bodies

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Biogenic Amines (BAs) are a group of molecules that act as neurotransmitters in the brain to modulate complex behaviors, including learning and memory formation. Drosophila melanogaster, an animal model with important genetic tools that shows similar mechanisms of neurotransmitter storage, release and recycling as compared to mammalian systems, has been extensively used in assays of aversive learning. In these protocols, a Pavlovian conditioning approach is used. For instance, an electric shock is applied

to flies (unconditioned stimulus, US) while they are exposed to an odorant (conditioning stimulus, CS). One of the open questions regarding this approach is what are the dynamic changes in fly brain neurotransmission during this conditioning. To answer this question, we generated a new system (fast scan cyclic voltammetry, FSCV) to measure the in vivo release of BAs in fly brain while the conditioning paradigm is carried out.

A single male fly was fixed to a recording chamber and the brain is exposed surgically. Using a carbon fiber electrode, we measured BAs release in the fly brain scanning from −0.4 to 1.2 V and back (vs Ag/AgCl reference electrode) at a scan rate of 400 V/s at 10 Hz. As positive control of identification and quantification of BAs, ATP-activated ion channels (P2X2 receptors) are expressed in specific aminergic neuronal populations and activated by ATP. To perform conditioning experiments, flies were exposed to a single electric shock every 5 seconds via an electric grid. In addition, we used a vacuum pump to deliver odorants.

We detected the release of BAs in the fly brain when ATP is applied. Release of octopamine, dopamine and 5-HT is detected within discrete structures of the brain in flies exposed to electric shock and mainly 5-HT is measured upon odorant stimulation. As negative control, no significant release of BAs is detected using a nominal zero calcium solution.

Our results show that we are able to measure the differential release of endogenous BAs in brains of flies exposed to stimuli relevant to olfactory learning and memory conditioning. Our data is consistent with the proposed role for the different amines in this process.

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Poster number: P-M138
Theme: Learning & memory

The Role of the Basal Ganglia in Memory Suppression and Motor Inhibition: Meta-Analysis and Dynamic Causal Modelling

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Memory suppression and motor inhibition share the cognitive process of active stopping. Previous research associated cortical activations with these forms of stopping. However, despite having a well-established role in motor control, the basal ganglia's involvement in memory suppression remains unexplored. Here we first tested the consistent activation of the basal ganglia in memory and motor stopping using a series of meta-analyses, and then investigated the role of the basal ganglia in these processes through dynamic causal modelling (DCM).

The meta-analyses included fMRI results from tasks requiring active suppression of prepotent thoughts or actions (e.g. Think/No-Think and Stop-Signal tasks), and revealed highly overlapping cortical and subcortical activations between memory and motor inhibition, including the right prefrontal cortex (DLPFC; VLPFC) and the basal ganglia. We then conducted the DCM effective connectivity analysis using a separate fMRI dataset that had participants performing the Think/No-Think and the Stop-signal tasks in one session. In the DCM models, we included both the putative domain-general regions (prefrontal cortex and basal ganglia), and the domain-specific regions (hippocampus for memory stopping, and primary motor cortex for motor stopping). We found that the basal ganglia were significantly involved in the network dynamics supporting the stopping processes in both tasks. Critically, it was the 'stopping' conditions that modulated the effective connectivity between the basal ganglia and the domain-specific regions instead of the retrieve/go conditions. These results provide strong evidence for a supramodal inhibition network in the brain, especially the novel indication that the basal ganglia play important roles in memory suppression in a similar fashion as in motor inhibition.

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Poster number: P-M139
Theme: Learning & memory

Reversal learning and the role of the primate mediodorsal thalamus

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Magnocellular mediodorsal thalamus (MDmc) contributes to adaptive decision-making and learning of object-reward discriminations, with thalamo-cortical interactions potentially mediating these cognitive processes. Prefrontal cortex dysfunctioning has been attributed to problems with response inhibition, as assessed by reversal learning paradigms. The current study investigated whether bilateral neurotoxic (NMDA/ibotenic acid) lesions to MDmc in macaque monkeys impact cognitive abilities due to deficits in response inhibition, using two different reversal learning paradigms. One paradigm involved learning 10 visual discriminations presented concurrently and repeated 20 times within the session. Once a 90% learning criterion was achieved, monkeys were exposed to reversals of the reward contingencies on subsequent sessions. The other paradigm involved learning a single visual discrimination presented serially for 100 trials in one session. All monkeys achieved 85% learning criterion within a single session, and on 12 subsequent test sessions, they were exposed to reversals of the reward contingency.

Monkeys with MDmc lesions demonstrated dissociable performance on the two reversal learning paradigms. Damage to MDmc caused impaired learning of the reversal in reward contingencies during concurrent presentation of the 10 visual discriminations compared to unoperated control animals. In contrast, during the serial reversal learning paradigm, overall reversal learning performance of monkeys with MDmc damage was not affected, although the monkeys were slower to adapt their choices after the first reversal of the reward contingency only. Our results suggest that deficits in cognitive performance after damage to the MDmc cannot be readily attributed to problems in response inhibition. Instead, our results suggest that interactions between the MDmc and interconnected cortex are critical to support the rapid integration of task relevant object-reward associative information, while response inhibition as measured in serial reversal learning paradigms is associated with interdependent neural networks of the brain.

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Poster number: P-M140
Theme: Developmental neuroscience

PREMATURE BIRTH WITHOUT INJURY DOES NOT PERTURB MURINE SENSIMOTOR DEVELOPMENT

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The preterm period coincides with rapid neurological development, during which neural migration and synaptogenesis result in the maturation of the thalamocortical pathways. As such it is postulated that prematurity results in disruptions in this development, affecting the connectivity of the infant brain, contributing to the neurological deficits seen clinically. This study uses a mouse model of prematurity to investigate the development of the sensorimotor pathways, at a synaptic, cellular and behavioural level.

Premature birth was induced in C57BL/6 female mice with a subcutaneous injection of the progesterone receptor antagonist RU486. Experiments were carried out on offspring during the first 3 postnatal weeks. Whole-cell patch clamp recordings of stellate neurons in acute barrel cortex slices were used to measure neuron membrane properties, excitability and miniature excitatory post-synaptic currents (mEPSCs). Anatomical development of the barrel cortex was assessed histologically using cytochrome oxidase (CO) staining. The development of reflexive sensorimotor behaviours were assessed with a battery of behavioural tests.

RU486 successfully induced preterm birth (mean gestation lengths: preterm = 18days±1.4 hours (n=29); control = 19days12±17hrs (n=21). $P < 0.0001$; two-tailed T-test)). Membrane properties and excitability of stellate cells showed developmental changes and the frequency of mEPSCs in the barrel cortex increased with age. However we found no differences between the development of these features in preterm and term pups. Assessment of thalamocortical neuron migration using CO staining showed that preterm and term pups followed the same developmental time course, with distinct barrels being visible by the end of the first postnatal week. Pups ability to complete tasks requiring sensorimotor coordination, such as righting reflex, and reflexive sensory behaviours such as whisking, improved with age, with preterm and term pups developing at the same rate. At weaning open-field testing showed no differences in exploratory behaviours in premature pups compared to controls.

Premature birth in mice raised in a normal environment does not alter the developmental trajectory of the sensorimotor pathway, on a synaptic, cellular or behavioural level

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Poster number: P-M141
Theme: Developmental neuroscience

VIP+ interneurons in the mouse barrel cortex during early postnatal development

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GABAergic interneurons (INs) are thought to have an important role in normal cortical circuit development. Recently we have shown that transient circuits involving somatostatin positive (SST+) cells assist in wiring the local columnar connectivity of the neonatal mouse somatosensory cortex (Marques-Smith et al., 2016). How this process co-ordinates with the formation of cross-modal cortico-cortical connections is however still unknown. A possible candidate for mediating such long range, early interactions could be vasointestinal peptide-positive (VIP+) INs. This population of IN are primary located in layers (L)2/3 (Prönneke et al., 2015), and known mediators of long-range cortico-cortical input in the mature cortex by preferentially targeting SST+ cells (e.g. Lee et al., 2013). Intriguingly unpublished data from the lab have identified L2/3 GABAergic synaptic input onto SST+ INs in whisker barrel cortex (S1BF) at early postnatal ages. We hypothesised that VIP+ cells in L2/3 are responsible for this GABAergic input and that they could have a role in coordinating long-range and local connectivity during early circuit development. We have employed optogenetics in combination with laser scanning photostimulation (LSPS) to confirm VIP+ IN input onto the SST+ cells within the first postnatal week. In parallel we have characterised early VIP+ cells using immunofluorescence, whole cell patch clamp and LSPS to dissect their cortical distribution, electrophysiological profiles and local glutamatergic inputs at these early ages. These data identify two populations of L2/3 VIP+ cell based on local synaptic connectivity. We hypothesis that these two populations differ in their long-range cortico-cortical inputs and regulation of SST+ IN signalling thereby playing distinct roles in circuit development.

Marques-Smith et al. (2016) A Transient Translaminar GABAergic Interneuron Circuit Connects Thalamocortical Recipient Layers in Neonatal Somatosensory Cortex. Neuron 89:536-49.

Lee et al. (2013) A disinhibitory circuit mediates motor integration in the somatosensory cortex. Nature Neuroscience 16:1662-70.

Prönneke et al. (2015) Characterizing VIP Neurons in the Barrel Cortex of VIPcre/tdTomato Mice Reveals Layer-Specific Differences. Cereb Cortex. 25:4854-68

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Poster number: P-M142
Theme: Developmental neuroscience

Resting state functional connectivity and network topology in Dyslexia genotypes

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Dyslexia is one of the most common neurodevelopmental disorders characterised by difficulties with accurate and fluent word recognition. Previous research has made significant progress into studying the behavioural, neuropsychological and neurobiological causes of the disorder. More recently, important understanding of the neural circuits and the aetiology of dyslexia came from respectively, brain imaging and genetics findings.

For example, PCSK6 is a gene that has been linked to handedness, brain asymmetry and developmental disorders including dyslexia (Brandler & Paracchini, Trends in Molc. Science, 2014). This study explores how the neurophysiological correlates of the reading impairment are related to dyslexia genetic risk, using resting-state magnetoencephalography (MEG). We compared resting-state functional connectivity and network topology of two groups (N=7) of dyslexic children, with (risk carriers) and without (risk-free group) risk allele at PCSK6.

By applying an atlas-based (AAL) MEG beamformer approach (Hillebrand et al., NeuroImage, 2012) we obtained a detailed anatomical mapping of neurophysiological patterns for different cortical rhythms. We used Phase Lag Index (PLI) to measure the resting-state functional connectivity. Subsequently, we reconstructed the functional network where each AAL based region (ROI) formed a node and each PLI value an edge.

Based on the functional network, the network topology for both dyslexia groups was estimated using weighted clustering coefficient (Cw) and path length (Lw) and compared via permutation testing.

We found that the two groups differ in connectivity strength at the PLI level and in cortical topology of individual edges (Lw) in salient regions of the reading network (left Superior Frontal, Inferior Parietal and Fusiform cortex), in delta (1-4Hz) and theta (4-8H) frequency bands.

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Poster number: P-M143
Theme: Developmental neuroscience

The effect of prenatal maternal immune activation on fetal development in a model investigating the developmental origins of schizophrenia

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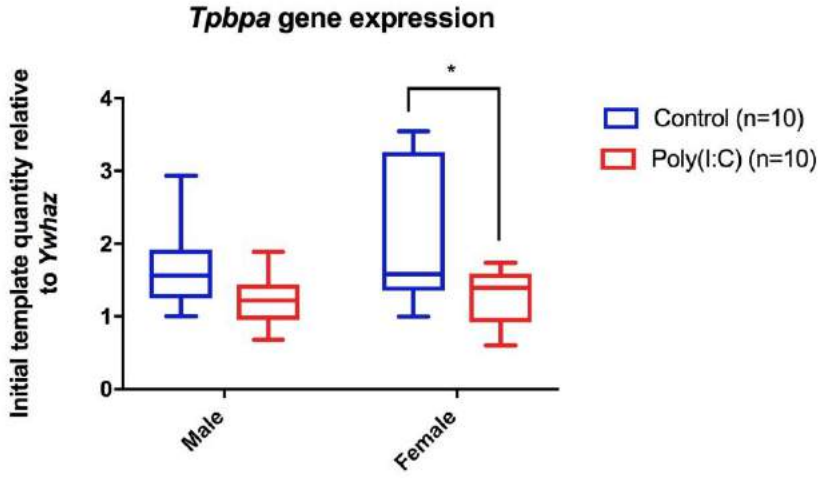
Introduction: Prenatal maternal immune activation (mIA) has widely been associated with the susceptibility of offspring to develop psychiatric disorders such as schizophrenia. This has been well characterised in terms of the maternal cytokine response elicited, the behavioural and cognitive changes in offspring and postnatal brain pathology in rodent models of mIA. This project specifically focuses on in utero changes in response to mIA, particularly in the placenta and yolk sac in a rodent model using poly(I:C) administration to induce mIA. We hypothesise that the placenta may be a critical mediator of developmental programming in schizophrenia, predominantly through alterations in its amino acid transporter activity.

Methods: A single intra-peritoneal injection of poly(I:C) or vehicle (10 mg/kg) was administered to pregnant female Wistar rats at GD15. Dams were sacrificed at two time points: GD16 and GD21 and two female and two male pups from each litter were randomly chosen for quantitative real time PCR analysis. Total RNA was extracted from the associated placentas and cDNA generated that was subsequently amplified using specific primers for Mapk1 and Stat3, system L transporter genes: Slc7a5, Slc7a8, Slc43a2, Slc3a2, placental cell-specific genes Gcm1 and Tpbpa and housekeeping gene Ywhaz. Placental expression changes of cytokines IL-6, TNF- α and IL-1β were also determined using the same method and protein level changes using ELISA.

Results: We show that poly(I:C) administration of GD15 had no significant effect on expression of system L transporter genes in GD21 placentas. We report a significant sex-specific (female) decrease in expression of Tpbpa, a marker of the placental junctional zone, at GD21 which suggests placental morphological changes in response to mIA, a finding also reported in models of fetal growth restriction. Ongoing work to be presented will further characterise cytokine changes and compare results between GD16 and GD21 time-points.



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Poster number: P-M144
Theme: Developmental neuroscience

The Effect of Maternal Immune Activation on Placental Gene Expression and Mother-Offspring Interactions in Rats

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Activation of the maternal immune system during pregnancy is a known risk factor for schizophrenia, thought to be caused by transient increases in maternal cytokines. Injection of the viral mimetic polyinosinic:polycytidylic acid (polyI:C) into pregnant rats during mid/late pregnancy causes a transient increase in maternal serum interleukin-6 (IL-6) levels and induces behavioural deficits in the adult offspring. Impaired placental transport of amino acids causes growth restriction and may underlie later life neurological deficits. For example, the solute carrier family 38a (Slc38a) transporters allow uptake of amino acids to the developing fetus. Methionine is an essential amino acid transported by Slc38a1, 2, and 4, and is used as a methyl donor for establishing and maintaining DNA methylation patterns. Emerging evidence from human and rodent studies supports a role for attenuated gene promoter methylation in schizophrenia. Maternal care in early postnatal life stably affects the epigenetic status of gene promoters in the offspring brain. We hence aim to investigate the effect of prenatal poly I:C treatment on the expression of the Slc38a family, DNA-methyltransferase-1 (Dnmt1), and immune genes in the rat placenta, as well as on the quality of mother-pup interactions in early postnatal life.

Female Wistar rats received a single intraperitoneal injection of 10 mg/kg poly I:C or vehicle at GD15 of pregnancy. For real-time quantitative PCR the dam and pups were sacrificed at GD21. Two male and two female pups were selected at random and total RNA was extracted from the corresponding placentas. 1µg of retrotranscribed cDNA was amplified using specific primers for the genes Slc38a1, Slc38a2, Slc38a4, Dnmt1, the Toll-like receptor-3 (Tlr3), Tlr5, and the housekeeping gene Ywhaz. For behavioural analyses, mother-pup interactions were scored live at postnatal days 6, 10, and 14.

We show that poly I:C treatment at GD15 has no effect on the expression of Slc38a transporter genes in the rat placenta. Poly I:C treatment induced a significant downregulation of Dnmt1 in female, but not male, placentas, suggesting a sex-specific change in DNA methylation. Upcoming work to be presented will assess the effect of poly I:C on maternal care and pup ultrasonic vocalisations.

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Poster number: P-M145
Theme: Developmental neuroscience

Computational modelling of ganglion cells growth in the retina

Authors: Jean de Montigny, Evelyne Sernagor, Roman Bauer*, Newcastle University, Institute of Neuroscience*

To understand how neurons grow and become integrated in neural networks, it is essential to investigate how the local environment influences these processes. We use the retina to study how coherent functional mature neural tissues emerge under the guidance of complex and dynamic developmental mechanisms including chemical signalling as well as physical interactions between cells (e.g. mechanical forces and electrical communication).

Computational modelling has been used to formalise and better understand the mechanisms involved in neuron growth (Graham and van Ooyen, 2007; Roberts et al., 2016). However, these studies are usually designed in a simplified context, without taking physical interactions into consideration. Here, we use the simulation framework Cx3D (Zubler and Douglas 2009) to computationally model the development of retinal ganglion cells (RGCs) in 3D physical space. RGCs play a key role in visual function, as they provide the only information channels between the eye and the brain, encoding all information about our visual world into trains of spikes sent to the brain via the optic nerve. A large number of RGC morphologies have been reconstructed and are publicly available.

In this study, we investigated the spatial growth of RGCs, and compared simulated morphologies with real RGCs available in the neuromorpho database (http://neuromorpho.org, Ascoli et al., 2007). We show how genetically encoded processes can yield complex and biologically plausible RGC morphologies by taking into account information available at the growth cone only, so without relying on a global supervisor. In particular, we demonstrate that a simple growth rule, named "2-thresholds growth rule", can explain a number of measures that we inferred from real morphologies (branching number, tip and branching distance, isometry and tree size).

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Poster number: P-M146
Theme: Developmental neuroscience

Regulation of mTORC1 signalling in neurodevelopment by the neuronal ceroid lipofuscinosis gene, CLN7

Authors: Kyle Connolly, *Institute of Cancer and Genomic Sciences University of Birmingham*

The neuronal ceroid lipofuscinoses (NCLs) are a group of inherited, childhood-onset, neurodegenerative diseases caused by mutations in CLN genes. Several late-onset neurodegenerative diseases show lysosomal dysfunction, and inherited lysosomal disorders often present with neurodegeneration, which, taken together, argues that maintaining lysosomal function is vital for neuronal health. However, neurodegeneration in the NCLs presents so early in life, it suggests that lysosomal function might also be required for normal neural development. We have been investigating this possibility in Drosophila models and demonstrate reduced neural development in mutants of CLN7, a gene mutated in late infant-onset NCL. CLN7 encodes a transmembrane protein thought to reside in the lysosomal membrane, and lysosomal function is essential for autophagy, a known regulator for neural development in Drosophila. However, the autophagy pathway is dependent on the inactivation of mTORC1 in the absence of growth stimuli and here we show that the developmental changes in CLN7 mutant synapses are not due to defective autophagy, but more likely due to hyperactivation of mTORC1 signalling. We demonstrate that the CLN7 protein is present in a complex with Rheb, an activator of mTORC1, and that loss of CLN7 function results in increased growth and reduced autophagy. We are now using Drosophila genetics to identify which signalling pathways require or impinge upon CLN7 function combined with a proximity-labelling proteomics approach to identify components of the CLN7 interactome. Together these will clarify the involvement of CLN7 in mTORC1 signalling and as a regulator of growth, autophagy and neural development.

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Poster number: P-M147
Theme: Developmental neuroscience

Histone acetylation and motor neuron regeneration in zebrafish spinal cord injury

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In contrast to mammals, zebrafish are capable of regenerating neurons in the central nervous system after an injury (1). For regeneration to occur, specific programmes of gene expression must be activated and modification of histone acetylation is one of the fundamental epigenetic mechanisms of gene expression changes. In particular, HDAC1 is essential for the regulation of two of the most important neurogenic pathway, Hedgehog and Notch, both of which are involved in motor neuron regeneration (2, 3). On this basis we decided to investigate the role of HDAC1 in motor neuron regeneration after spinal cord injury in zebrafish larvae.

We find that HDAC1 mRNA is upregulated in ependymo-radial glial cells (ERGs), the spinal progenitor cells, after an injury. We then used both pan and selective HDAC1 inhibitors to treat larvae after spinal cord transection, showing that inhibitor-treated larvae displayed a lower number of regenerated Hb9+ motor neuron after the lesion.

Recent findings in our group indicate that fish treated with immunosuppressant drugs (5) also fail to regenerate motor neurons. We demonstrate that in fish larvae lacking microglia and macrophages, HDAC1 is not upregulated after spinal injury. Conversely, triggering the immune system with LPS (in the absence of a lesion) is sufficient to induce HDAC1 expression in ERGs. This suggests that HDAC1 upregulation is controlled by the immune response after injury. In conclusion, we present evidence that HDAC1 plays an important role in the neuroregenerative process observed in zebrafish larvae after a spinal cord injury and that HDAC1 expression might be regulated by immune system activation.

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Poster number: P-M148
Theme: Developmental neuroscience

Utilising human patient iPSC derived neurons to uncover cellular and network neurodevelopmental phenotypes in autism spectrum disorders

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Autism spectrum disorders (ASD) are a group of complex, genetically heterogeneous neurodevelopmental disorders characterised by impairments in communication and social behaviour as well as a propensity to engage in repetitive behaviours. ASD ranges in severity from having a mild impact on day-to-day life to the need for constant care, often presenting with multiple neurological and neuropsychiatric comorbidities such as intellectual disability, developmental delay and epilepsy. Despite the fact that global prevalence is estimated at 1-2%, both their aetiology and pathophysiology are poorly understood and no medicines addressing the core symptoms currently exist.

Research into cellular and developmental mechanisms responsible for ASD has been hindered by a lack of reproducible cellular models that have construct validity. Induced pluripotent stem cell (iPSC) technology allows neural precursor cells (NPCs) and neurons sharing the same genetic background as living human patients to be grown in a dish, providing unique insight into cellular and network neurodevelopment.

Caused by maternal origin duplications or triplications of the notoriously unstable chromosomal region 15q11.2-13.1, 15q11-13 duplication syndrome or ‘dup15q’ is the most common known cytogenetic cause of ASD (Hogart et al., 2010). The link between genotype and phenotype is currently unknown, although the 15q11-13 region notably contains a cluster of GABAA subunit genes (alpha 5, beta 3 and gamma 3) as well as the ubiquitin E3 ligase UBE3A, whose function is lost in Angelman Syndrome.

In the present study, NPCs and neurons were produced from iPSCs reprogrammed from a patient with dup15q and a neurotypical first-degree relative. They were characterised with extracellular microelectrode array recordings, whole cell patch-clamp and quantitative immunohistochemistry. These results are indicative of pronounced network GABAergic dysfunction as well as altered subunit composition of the GABAA receptor, consistent with reports of lack of benzodiazepine efficacy in treating seizures in dup15q patients. We also report a two-fold increase in NPC numbers, which may be a product of disruptions in proliferation and differentiation relating to the early developmental role of GABA transmission.

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Poster number: P-M149
Theme: Developmental neuroscience

Genetic labelling of synaptic diversity in the mouse hippocampus during development

Authors: Vlad Anton, Zhen Qiu,Melissa Cizeron, Noboru H. Komiyama, Seth G. N. Grant, *Centre for Clinical Brain Sciences University of Edinburgh*

The postsynaptic density (PSD) of excitatory synapses in the vertebrate central nervous system contains a conserved set of ~1,000 proteins and mutations in these cause over 130 brain diseases (1). PSD95 is a scaffold protein that organizes a family of multiprotein supercomplexes, some of which contain NMDA receptors. SAP102 is a paralog of PSD95 and organises distinct multiprotein complexes (2). The differential distribution of complexes into different synapses provides structural and functional diversity to synapses.

To study the distribution and diversity of complexes and we have used a genetic labelling technique that permits us to visualize PSD95, SAP102 and the NMDA receptor GluN1 subunit. The endogenous genes for these proteins were modified by gene targeting to create fusion proteins: PSD95-eGFP, SAP-mKO2 and GluN-FLAG, which can be visualized at the individual synapse level using fluorescence microscopy. The hippocampus, a hub of synaptic diversity, was examined using a spinning disk confocal microscope on fixed brain sections from 36 mice across 7 age groups (postnatal day 1 to 95). Advanced image analysis allowed the unsupervised classification of over 40 synapse subtypes based on the morphological features of these three protein markers.

Researchers are becoming increasingly aware of the importance of the synaptic diversity that arises from the combinatorial assembly of synaptic proteins (3). Our work primarily establishes a framework for the quantitative analysis of synaptic diversity and warrants caution when interpreting results of bulk measurements like western blotting, mass spectrometry and many electrophysiological techniques. Beyond this, correlating the trajectories of individual synapse subtypes with known developmental processes could provide insight into their functional roles. Studying the effects of diseases (in disease models) on specific subtypes could also reveal the function of synaptic subtypes, in addition to broadening our understanding of disease mechanisms and aiding drug targeting.

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Poster number: P-M150
Theme: Developmental neuroscience

Effects of 5HT1A and 5HT7 receptor signalling on development of rat cortical neurons

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The interaction of the neurotransmitter serotonin (5-HT) with its receptors (5-HTR) plays a diverse regulatory role on neural plasticity, including during early development, which has been implicated in the aetiology of various behavioural disorders. 5-HT1A and 5-HT7 receptors are both activated by the serotonergic agonist 8-OH-DPAT and exert their modulatory roles via interaction with a range of signalling cascades, notably through opposing effects on cAMP production. Contrasting reports of 8-OH-DPAT effects in different cell types could be due to complex interactions of these two 5-HTRs on neural development. We suggest that the interplay of 5-HT1AR/5-HT7R activity provides a mechanism that contributes to the overall modulation of cortical neurite growth.

This has been investigated using primary rat cortical cultures as a model system to study the role of 5-HT1AR/5-HT7R expression and the differential roles of their signalling cascades on neurite growth. As a first part of this study, we show that chronic application of 8-OH-DPAT (5 µM) causes a significant increase in the average dendrite length per neuron by 38±14% compared to control cultures (1-way ANOVA followed by Tukey post-hoc test: $p<0.05$; 18-19 coverslips from 2 independent cultures per condition). The growth promoting effect of 8-OH-DPAT is completely abolished by the co-application of the 5HT7R antagonist SB-269970 (1 µM; 8-OH-DPAT vs 8-OH-DPAT + SB-269970: $p=0.05$; control vs 8-OH-DPAT + SB-269970: $p=1.0$). In contrast, SB-269970 on its own has no significant effect on average neurite growth ($p=0.99$) indicating that its effect is due to inhibition of 8-OH-DPAT-activated 5-HT7R mediated signalling. This data strongly suggests that 5-HT7R mediated signalling, rather than 5-HT1AR signalling,

plays a significant role in modulating cortical neuronal growth. However, it does not preclude the possibility that 5-HT7R mediated effects on cortical development can be modulated by direct interactions between 5-HT7R and 5-HT1AR.

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Poster number: P-M151
Theme: Psychiatry & mental health

Reduced neural reward bias in major depression disorder using a fMRI probabilistic reinforcement learning task

Authors: Alexandra Antonesei, Sally-Anne Marie Vincent, Kou Murayama, Ciara McCabe – *Psychology, University of Reading*

Anhedonia, one of the two main clinical symptoms in major depression disorder (MDD), has been experimentally related to deficits in reinforcement learning. The reward deficit may point towards a dopaminergic imbalance, e.g, blunted neural activation in ventral striatum, caudate and less consistently in orbitofrontal cortex (OFC). In a behavioural probabilistic learning task based on a differential reinforcement schedule using virtual money, MDD patients showed reduced reward learning compared to healthy controls (HC). The aim of this study was first to adjust the reinforcement learning behavioural task to the scanner environment; and secondly to test the effects of different reinforcement ratios of rewarding taste stimuli at neural level in MDD vs HC.

Methods: 59 participants (N=26 MDD, N=33 HC) took part in a probabilistic learning task inside the scanner. In a three-block event-related design, participants had to distinguish between two highly similar stimuli, while trying to maximize the intake of chocolate reward. Unknown to the participants, chocolate reward was delivered four times more for one stimulus (target) compared to the other one (non-target). Reward bias refers to the participants' tendency to define an ambiguous stimulus as target.

Results: Preliminary analyses showed less BOLD activation in MDD vs HC in the left caudate ($p<.05$, FWE for multiple comparisons) in response to the target vs non-target contrasts, and in the anterior cingulate cortex ($p<.05$, FWE for multiple comparisons) in response to the target vs missing the target contrasts. However, MDD vs HC showed increased BOLD activation in the OFC/insula ($p<.05$, FWE for multiple comparisons) in response to the target vs the bias contrasts.

Conclusions: In line with previous research, MDD participants with anhedonia symptoms showed decreased activation to rewarding stimuli in reward areas of the brain. Moreover, MDD compared to HC showed increased OFC activation when spotting the difference between the target and the ambiguous stimulus. Results of this task show that at the brain level, MDD compared to HC are better at differentiating between a rewarding and an ambiguous stimulus, while showing a conservative response in defining other stimuli as rewards.

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Poster number: P-M152
Theme: Psychiatry & mental health

DLG2, neural development and neuropsychiatric disease

Authors: Bret Sanders - *Neuroscience and Mental Health Research Institute Cardiff University*

Discs large homologue 2 (DLG2) is a membrane associated guanylate kinase (MAGUK) protein located in the post synaptic density (PSD) of neuronal synapses, here it acts as a scaffold to regulate receptor clustering and intracellular trafficking through associations both with other proteins and the actin cytoskeleton. Disruptions to the DLG2 gene such as in the 11q14.1 copy number variant (CNV) have be associated with neuropsychiatric disease, specifically an increased risk of schizophrenia, although the genotype to phenotype relationship is incompletely understood. Preliminary data showing DLG2 expression in neural precursor cells (NPCs), a much earlier stage of neural development than previously reported, indicates that the role of DLG2 extends beyond synaptic function. Here the results of ongoing experiments to verify these data by analysing the endogenous pattern of DLG2 expression throughout neural development are reported, using human embryonic stem (hES) cells differentiated to cortical projection neurons as a model system. As available anti-DLG2 antibodies exhibit both inconsistent binding to DLG2 isoforms and unspecific binding to other proteins CRISPR/Cas9 technology was used to generate tagged DLG2, enabling the spatial and temporal pattern of DLG2 expression to be determined through immunocytochemistry. Additionally DLG2 deficient hES cells along with wild-type (WT) controls were differentiated to cortical projection neurons and the phenotype of these cells characterised at various stages of neural development through staining for neural markers, using both immunocytochemistry and western blotting. Although these data are not fully analysed they suggest DLG2 is required for normal cortical projection neuron development. It is expressed in

NPCs and likely has a role in regulating early neural development. DLG2 deficient neurons show a disruption to cortical layer markers providing further evidence for a key neurodevelopmental role for DLG2 and a potential link to neuropsychiatric disease.

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Poster number: P-M153
Theme: Psychiatry & mental health

Prefrontal influences on the motor system modulate volitional action in Tourette Syndrome

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Introduction
People with Tourette Syndrome (TS) experience 'unwilled' hyperkinetic movements known as tics. Despite the compulsive nature of tics, adults with TS can often exercise volitional control over whether to release or suppress a tic. Evidence from neurotypical populations suggests that control of actions proceeds via prefrontal modulation of cortico-subcortical interactions with the basal ganglia (Rae et al, 2015, J Neurosci). We tested how prefrontal regions influence the basal ganglia and motor cortex in TS, and how this shapes voluntary action decisions.

Methods
23 adult participants with TS (13 male; age 18-51, mean 34) and 22 matched controls (12 male; age 19-55, mean 34) underwent fMRI during an intentional inhibition task. 750 T2*-weighted echo planar images were acquired on a 1.5T Siemens Avanto (34 slices, 3x3x3.6mm resolution, TR = 2520ms, TE = 43ms). fMRI pre-processing and general linear modelling was run in SPM12 (www.fil.ion.ucl.ac.uk/spm). The intentional inhibition task required participants to press a button in response to a green cue (go, 50% trials), withhold their response to a red cue (nogo, 16%) and choose whether to press or not in response to a yellow cue (choice, 34%).

Results
Interaction contrasts suggested that compared to controls, participants with TS showed reduced activity in preSMA when choosing to move (choose-go) compared to instructed to move (go); greater activity in inferior frontal gyrus when withholding actions (choose-nogo and nogo); and greater activity in M1 when choosing to withhold an action (choose-nogo) (Figure 1). Dynamic Causal Modelling was applied to determine the influences of preSMA and inferior frontal gyrus on subcortical nuclei and M1.
Conclusions
When choosing to make or withhold voluntary movements, people with TS require less neural activity in motor preparation areas to produce actions; require greater neural activity in motor control areas to withhold actions; and even when withholding actions, suppress primary motor cortex activity to a lesser extent. These results suggest dysfunctional outflow of motor signals from basal ganglia can be modulated by prefrontal influences to determine action decisions. This may underpin the tic suppression strategy often employed by people with TS.

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Poster number: P-M154
Theme: Psychiatry & mental health

Corticostriatal Dysregulation as a Risk Endophenotype in Bipolar Disorder

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Aims:
Bipolar disorder is a highly heritable condition in which there is dysfunction of corticostriatal circuitry. This study aimed to elicit whether functional changes to corticostriatal circuitry represent a risk endophenotype for the condition. We aimed to achieve this via the medium of resting-state functional magnetic resonance imaging (rs-fMRI).

Methods:
38 bipolar disorder patients were recruited, 32 unaffected first-degree relatives and 23 healthy controls. Groups were demographically well matched. Initially, rs-fMRI data was appropriately cleaned using typical methods. A seed-based analysis was then run using left and right nucleus accumbens regions-of-interest.

Results:
A ventral-dorsal gradient was observed in corticostriatal correlation whereby ventral prefrontal cortex showed increased correlation with the nucleus accumbens and dorsal prefrontal cortex showed increased negative correlation with the nucleus accumbens ($p<0.05$). This finding was present in both patients compared to controls and relatives compared to controls and as such signifies a risk endophenotype.
Conclusions:
This study identified a risk endophenotype for Bipolar Disorder. This profile of changes to corticostriatal function predispose an individual to developing the disorder, but they're not directly correlated with symptoms or caused by them. Future work could utilise this endophenotype in a clinical setting to improve patient outcomes.

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Poster number: P-M155
Theme: Psychiatry & mental health

Changing trends in antidepressant prescribing to children in UK primary care, 2000 – 2015

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Antidepressant prescribing in children and adolescents increased steadily in the United States and parts of Europe between 2005 and 2012 despite regulatory safety warnings. Little is known about the characteristics of those being prescribed antidepressants for the first time and their treatment course.

A longitudinal study of 3-17 year olds prescribed antidepressant for the first time in primary care was carried out using routinely collected anonymised primary care data from the UK Clinical Practice Research Datalink (CPRD) between 2000 and 2015. Changes in the incidence of first ever antidepressant prescriptions and the characteristics of those being prescribed them was examined. As prescriptions are not directly linked to the indication they were prescribed for in the CPRD linkage was inferred by temporal proximity.

Incidence of first ever prescriptions nearly doubled between 2006 and 2015 rising from 1.60 (95%CI: 1.51, 1.69) to 3.12 (3.00, 3.25) per 1000 person years, with females more than twice as likely as males to be a recipient of one of these prescriptions. Only 21% of the 1721 patients with incident prescriptions in 2015 could be linked to a depression diagnosis, with an additional 22% of prescriptions linked to alternative indications. The incidence of prescriptions linked to a depression diagnosis increased between 2012 and 2015, with an adjusted incidence rate ratio of 1.46 (1.26, 1.70). Overall antidepressant prescribing increased most rapidly in 15-17 year old females.

Antidepressant prescribing in children increased between 2006 and 2015. This is, at least in part, due to a rise in alternative uses of antidepressants, including the treatment of anxiety, chronic pain and migraines.

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Poster number: P-M156
Theme: Psychiatry & mental health

Limbic-cortical network activity and behaviour in a novel Cyfip1 genetic rat model of psychiatric risk

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Cyfip1 gene dosage is reduced in 15q11.2 deletion syndromes, which are associated with a range of psychiatric symptoms. The neural bases of these symptoms are unknown, but abnormal functional connectivity between the frontal and temporal lobes

features in other psychiatric patients and genetic risk factor carriers, in other rodent models, and is increasingly thought to contribute to cognitive deficits. We are using a novel line of Cyfip1 heterozygous knockout rats (Cyfip1±) to define the consequences of Cyfip1 knockdown for brain function and behaviour.

We trained 7 wildtype (WT) and 4 Cyfip1± littermates on a rewarded alternation T-maze task which invokes working memory, an aspect of cognition consistently impaired in psychiatric disorders. Chronically implanted microelectrode arrays were used to simultaneously record local field potentials (LFP) from dorsal CA1 of the hippocampus (CA1) and medial prefrontal cortex (PFC).

Cyfip1± rats tended to run fewer trials per 40min session (WT 27±2 trials, Cyfip1± 20±3; p=0.08), typically making more hesitant runs down the central arm of the maze, rather than continuous runs to the reward point (% of hesitant runs: WT 16±4, Cyfip1± 55±17; p=0.08). Choice accuracy, however, was normal (WT 79±4%, Cyfip1± 88±5%, p>0.05).

Considering only trials with continuous runs, LFP spectral profiles appeared normal in Cyfip1± rats, which showed CA1 and PFC 5-10Hz theta amplitudes similar to WT. This suggests that local networks remain broadly intact in Cyfip1± rats.

However, using spectral coherence to infer functional interactions between CA1 and PFC suggested that theta coherence in Cyfip1± rats was more sensitive to cognitive context compared to in WT. The difference in coherence between guided and choice turns on the T-maze was significantly higher in Cyfip1± than WT ($p<0.05$). This result is reminiscent of an fMRI study in which schizophrenia risk allele carriers showed increased coupling between PFC and HPC, with no impact on task performance (1).

These findings indicate that impaired neural network activity during a working memory task is a consequence of reduced Cyfip1 gene dosage, and may be an important component of the pathophysiology underlying psychiatric conditions.

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Poster number: P-M157
Theme: Psychiatry & mental health

Early Developmental Disturbances in Cortical Folding are Associated with Persistence of Psychotic Experiences

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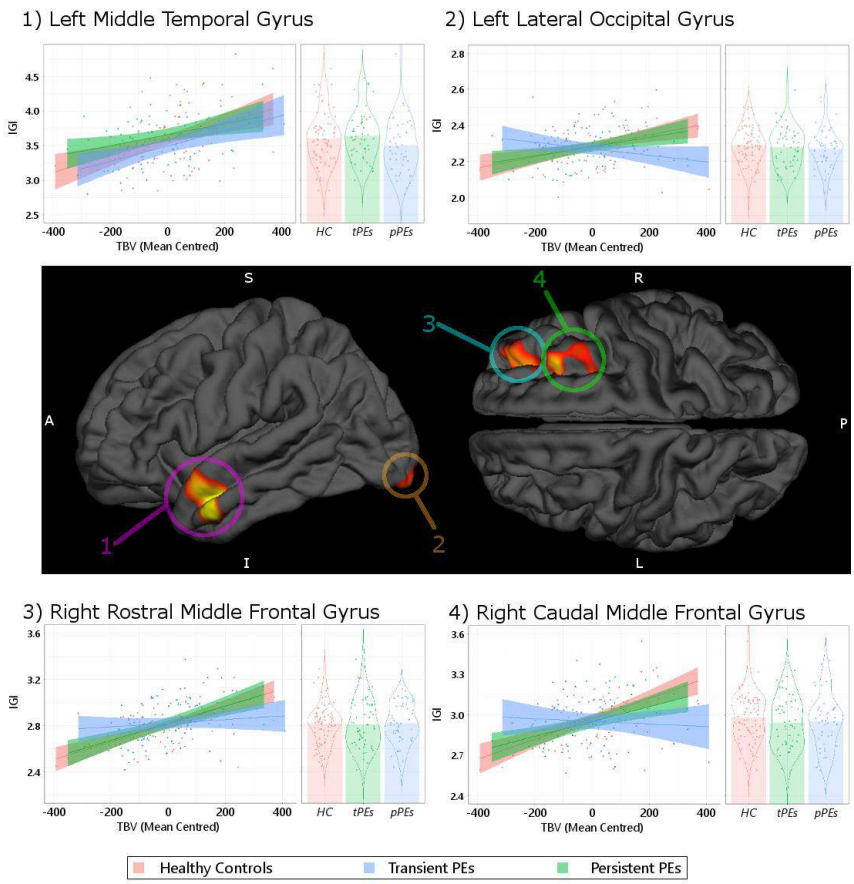
The expression of psychotic phenomena such as hallucinations and delusions has been proposed to lie along a continuum and subclinical manifestations are more prevalent in the general population. These psychotic experiences (PEs) are typically transient in nature, but are associated with an elevated risk of transition to psychosis that further increases with persistence of PEs. Onset of PEs typically occurs during adolescence and shares many aetiological factors with schizophrenia. Here, we sought to assess the utility of PEs in psychosis research by examining cortical morphometry in relation to transient and persistent PEs; assuming comparable alterations in morphometry represent a vulnerability to psychosis and should be observable. Additionally, we sought to differentiate the effects of high genetic risk by including a polygenic risk score for schizophrenia.

Imaging data were acquired on 247 young adults who were assessed for PEs at ages 18 and 20. Surface maps of gyrification (lGI) and cortical thickness (CT) were computed using Freesurfer. Individuals with PEs at both assessments (persistent PEs) showed reduced lGI in the left middle temporal gyrus as well as reductions in lGI with increasing brain volume (TBV) in left lateral occipital and right middle frontal gyri. No main effect of polygenic risk for schizophrenia (PGRs) was found. Including both PEs and the PGRs did not change our findings and identified reductions in lGI with increasing PGRs in the left medial orbitofrontal gyrus for persistent PEs and in left inferior parietal and postcentral gyri for transient PEs.

The location of disturbances in lGI was similar to schizophrenia but effects were limited to persistent PEs. No effect was found for the PGRs but there were conflicting effects with PEs. There was no evidence of deterioration in thickness or volume. Gyrification is considered a marker of early neurodevelopment and the atypical associations between lGI and TBV could reflect early disturbances in cortical expansion that reflect a premature plateauing in those with persistent PEs. However, we cannot exclude the possibility of progressive changes towards a psychotic disorder.



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Poster number: P-M158
Theme: Psychiatry & mental health

Differences in cortical thickness between patients with Non-Epileptic Attack Disorder and healthy controls

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Objective: We report preliminary findings of a study intended to improve the biopsychosocial understanding of Non-epileptic Attack Disorder (NEAD) and help destigmatise the condition by exploring its neurobiological basis. We compared structural magnetic resonance imaging (sMRI) of patients with NEAD and healthy controls (HCs). Two previous sMRI studies of patients with NEAD have yielded conflicting results with one reporting predominantly right hemispheric changes in NEAD (NEAD group n = 20, HC group n = 40) and the other bilateral changes (NEAD group n = 37, HC group n = 37) .

Method: T1 weighted 3T sMRI brain scans of patients with NEAD (n = 30, 23 female, mean age = 40.13, range = 18 to 75) and age and gender matched healthy controls sMRI brain scans (n = 30, 23 female, mean age = 39.37, range 19 to 65) acquired between 2009 and 2016 were retrieved retrospectively and automatically segmented using FreeSurfer (v. 5.3.0). Group differences for cortical thickness (CT), volume (V), cortical surface area (CSA), cortical folding (CF), and sulcal depth (SD) were examined using the built in GLM FreeSurfer utility (QDEC, v. 1.4), controlling for age, gender and intracranial volume. Results were corrected for multiple comparisons using FDR at $p < 0.01$.

Preliminary Results: Compared to HCs, patients with NEAD showed distinct bilateral structural abnormalities with decreases in CT in both the left and right superior temporal brain regions as well as left inferior frontal (pars opecularis) and the right superior frontal gyri. Greater CT was observed in the left and right paracentral lobules, left and right parietal cerebrum, as well as left and right occipital regions. In addition, patients with NEAD showed decreases in volume in the left pars triangularis. No significant differences between the groups were found for CSA, CF or SD.

Conclusion: We identified significant differences in cortical structure of bilateral frontal, parietal, temporal and occipital brain regions between individuals with NEAD and healthy matched controls. These areas are involved in higher cognitive functions, emotion processing, and motor function. While some of the observed changes are consistent with previous research, others differ, perhaps reflecting the heterogeneity of NEAD.

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Poster number: P-M159
Theme: Psychiatry & mental health

Kainate receptors and brain disorders: New potential therapeutic avenues

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Kainate receptors (KARs) are ionotropic glutamate receptors involved in presynaptic and postsynaptic neurotransmission mechanisms. They form functional ion channels by tetrameric combinations of five different subunits (GRIK1-GRIK5, GluK1-GluK5) modulated by auxiliary proteins Neto1 and Neto2. We hypothesize that functional genetic variants within human KAR and Neto genes contribute to risk or protection for developing neuropsychiatric disorders such as mood disorders, psychosis, and autism spectrum disorder [1].

This study investigated how genetic risk factors and pharmacological compounds affect KAR ionic function and may contribute to disease. Using the UK10K cohort datasets, we performed bioinformatics analysis of next generation sequencing data of unaffected individuals and individuals with psychiatric disorders and learning disabilities. We also performed electrophysiological studies using Xenopus oocytes expressing cloned human KAR and Neto transcripts and treatments with pharmacological compounds. We report the identification of a number of rare, predicted damaging, missense mutations found exclusively in case populations. We provide further evidence of the protective role of a GRIK4 indel against cognitive decline. We also report GluK2 and GluK2/GluK4 subunits sensitivity to agonist and antagonist (ketamine, citalopram) compounds and their decay kinetics with and without co-expressing Neto1 and Neto2.

Our current findings support the hypothesis that genetic variation within KARs and Neto genes may contribute to neuropsychiatric phenotypes and that antidepressants/antipsychotics can alter the electrophysiological properties of KARs. This research will provide a better understanding of the link between genetic risk, biological processes and potential therapeutic avenues for brain disorders.

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Poster number: P-M160
Theme: Psychiatry & mental health

Electrophysiological properties of the hippocampus-medial prefrontal cortex pathway in the sub-chronic phencyclidine model for schizophrenia

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Introduction The functional coupling between the ventral hippocampus (VH) and medial prefrontal cortex (mPFC) is essential for context dependent memory retrieval, working memory and goal directed behaviour. Disruption to VH-mPFC in schizophrenia (SZ) is thought to be responsible for deficits in these cognitive processes (Godsil et al., 2013, Eur Neuropsychopharm 23, 1165–1181). However, the underlying mechanisms for this remain relatively unexplored. In this study, we address this by assessing synaptic plasticity and functional connectivity between VH-mPFC in the sub-chronic phencyclidine (scPCP) model of neurocognitive deficits in SZ.

Methods 27 adult female Lister_Hooded rats were randomly assigned to receive intraperitoneal (i.p) injection of PCP-HCl (2 mg/kg, n=15) or vehicle (0.9% saline, n=12) twice daily for 7 days, followed by 7 days of washout. The novel object recognition (NOR)

performance was assessed twice, once before the start of the electrophysiological work and once half way through in remaining rats to confirm persistence of the deficit. Electrophysiological recordings were obtained under urethane anaesthesia (30% w/v, 1.5 mg/kg, i.p). Spontaneous neural oscillations were recorded from electrodes in mPFC and VH to investigate phase-locking patterns between the two regions. Following replacement of the VH recording electrode with a stimulating electrode, VH-evoked mPFC responses were recorded to assess short/long-term synaptic plasticity and functional connectivity.

Results The vehicle-treated rats explored the novel object significantly more than the familiar object when tested at both time-points ($P<0.05$). This ability was lost in the scPCP treated rats when first tested ($p=0.38$) and at the second time-point ($p=0.056$). Electrophysiological results from VH-mPFC will be presented from these behaviourally characterised rats.

Conclusion Understanding the mechanisms underlying altered VH-mPFC communication in SZ will help our understanding of cognitive deficits associated with the disease. Here, a persistent cognitive deficit in scPCP rats suggests that the desired pathology is established. Hence this model is suitable for investigating this circuitry as a potential therapeutic target for cognitive dysfunction in SZ and similar disorders.

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Poster number: P-M161
Theme: Psychiatry & mental health

Trait Related Aberrant Connectivity in First Episode Schizophrenia

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Background: Findings in functional connectivity in schizophrenia have so far been inconclusive with some studies reporting hyper-connectivity in the major resting state networks while others report hypo-connectivity. Of particular interest is the role of the Lingual Gyrus in schizophrenia which shows increased connectivity and is a reliable predictor for development of the disorder in at-risk individuals. In this study we used a seed based functional connectivity analysis to investigate how brain networks emerge in the brains of First Episode Psychosis (FEP) patients who are symptomatologically stable, and assess Lingual Gyrus connectivity.

Methods: Twenty FEP patients in a stable phase of their illness and 20 healthy controls were recruited. All the participants underwent resting-state functional Magnetic Resonance Imaging (rs-fMRI). The Data Processing Assistant for Resting-State fMRI Advanced Edition (DPARSFA) V3.1 (http://rfmri.org/DPARSF) (Yan & Zang, 2010) and the statistical parametric mapping software 8 (SPM8) (SPM, Friston, The Wellcome Department of Cognitive Neurology, London, Uk; http://www.fil.ion.ucl.ac.uk/spm) were used to preprocess and analyze the data.

Results: FEP patients exhibited deficient connectivity in the major resting-state networks (Default Mode Network, Executive Control Network, Salience Network) compared to healthy controls, albeit at a statistically not significant level. The Lingual Gyrus of FEP patients revealed increased connectivity in comparison to healthy controls with the Middle Frontal Gyrus, and the Cingulate Cortex.

Conclusions: Our findings suggest that deficient connectivity in resting-state networks is disorder generated and reversible. Lingual Gyrus connectivity appears to be a stable resilient trait neuroimaging marker for psychosis.

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Poster number: P-M162
Theme: Psychiatry & mental health

Cognitive Impairment in Opiate and Psychostimulant Addiction

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AIM
It has been widely reported that opiate and psychostimulant addiction in humans is associated with substantive cognitive impairment. However, it remains unclear which cognitive domains are most severely affected. This has fundamental implications for the theory and treatment of addiction. We therefore conducted a random-effects meta-analysis.

METHODS:
We systematically searched the Web of Knowledge suite and PubMed database, using the Taporware text analytics tool to optimise these searches. Searches were completed on 16th December 2015 and identified a total of 12,028 papers. Data that satisfied our a priori inclusion criteria were assigned to one of the following four cognitive domains: Language, Motor, Memory and Executive Function; each of these domains were further divided into sub-domains. Ultimately, we included 65 studies and data from 2752 users and 2356 healthy control participants. Following data extraction, random-effects meta-analyses were performed using Stata 14.

RESULTS:
Cognitive impairment was associated with opiate or psychostimulant abuse across all domains, though this did not reach statistical significance in some sub-domains: for opiate users, Verbal Comprehension, Verbal Declarative Memory and Auditory Declarative Memory; for psychostimulant users, Psychomotor Performance and Attention. The general trend across domains was for impairment to be more severe in opiate users than in psychostimulant users (Opiates, SMD = -0.68; P=<0.000; Psychostimulants, SMD = -0.43; P=<0.000), but there were notable differences between sub-domains. Specifically, the most substantial impairment shown in opiate users was in Visual Declarative Memory (SMD= -1.84; P=0.000). The most substantial impairment shown in psychostimulant users was in Verbal Comprehension (SMD = -1.17; P=0.000). Impairments in Impulse Control were modest in opiate (SMD = -0.48; P=0.000), and psychostimulant users (SMD = -0.35; P=0.000).

CONCLUSIONS:
There are substantive differences in the forms of cognitive deficit associated with psychostimulant and opiate use. This challenges some currently influential theories of drug addiction, and has immediate implications for treatment.

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Poster number: P-M163
Theme: Psychiatry & mental health

Molecular and behavioural characterisation of schizophrenia risk gene DLG2 rodent models

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Rare, but highly penetrant, mutations increase the risk of developing schizophrenia. There is significant convergence of these mutations on synaptic signalling pathways. Scaffolding protein Discs, large homolog 2 (DLG2) is vital to post-synaptic density (PSD) function. The PSD mediates pre- and post-synaptic membrane apposition, post-synaptic receptor clustering and couples receptor activation to intracellular signalling cascades. De novo copy number variants spanning DLG2 are associated with increased risk of schizophrenia. DLG2-/- mice show impaired reversal learning, objection-location paired association, extinction, aversive learning and attention. The current study utilises DLG2+/- mice and rat models, which more closely mimic the heterozygous human deletion. Initial work focused on gene dosage confirmation and basic behavioural assessment. DLG2+/- mice displayed no abnormalities of motor function, prepulse inhibition of startle, or anxiety, but had a significant motor learning deficit and a trend towards a habituation impairment in acoustic startle responses. We also explored adulthood neurogenesis, in the dentate gyrus, proposed as a dysregulated plasticity mechanism underlying the cognition symptoms in schizophrenia. Neurogenesis abnormalities have been described in several schizophrenia risk gene models. In contrast we found no differences in newborn neuron numbers in 8-week-old DLG2+/- mice. Both analysis of newborn neuronal survival from 8 weeks and the impact of age and behavioural tasks on proliferation in 8 month old mice will be presented. The project is now focusing on homeostatic plasticity mechanisms. DLG2 interacts with two key receptors in this process, NMDA and AMPA. Dark rearing (binocular visual deprivation) provides a reliable model for assessing homeostatic plasticity. Initial analysis of key synaptic protein expression in juvenile DLG2+/- and DLG2-/- mice will be presented. Future investigations of PSD associated protein expression after the critical period for visual cortex development, and hippocampal contextual fear conditioning, in the DLG2 models will elucidate the extent to which impairment of plasticity mechanisms, dependent on PSD function, contribute to the cognitive deficits seen in psychiatric disorders.

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Poster number: P-M164
Theme: Psychiatry & mental health

Amygdala responses to fear associated with individual differences in circadian rhythm

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Heightened amygdala responses towards negative emotional stimuli have been observed in individuals with depression. Previous research has demonstrated that similar negative biases are present in high risk individuals even in the absence of a personal history of depression, thereby suggesting they may reflect a neural vulnerability marker. The current study aimed to investigate amygdala responses to fearful facial expressions in a novel at risk group – namely late chronotypes. It was hypothesised that late chronotypes would show elevated amygdala responses towards fearful facial expressions compared to early chronotypes. Seventeen participants underwent functional magnetic resonance imaging (fMRI) whilst completing an implicit facial expression task. Participant sleep quality and mood was also assessed. A significant negative correlation was observed between the amygdala blood oxygen level dependent (BOLD) signal and chronotype score (rMEQ). In conclusion, late chronotypes show altered responses to emotional stimuli which may, in part, mediate the vulnerability of these individuals to depression.

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Poster number: P-M165
Theme: Methods and techniques

OpsLib – a library of parameterised opsin models

Authors: Benjamin Evans, Konstantin Nikolic - *Institute of Biomedical Engineering Imperial College London*

Since its inception, optogenetics has rapidly flourished as a method, for probing and modulating the function of neurons and other excitable tissue. So far, genes for optogenetic actuators (opsins) have been isolated and harnessed from several families of organisms including algae, bacteria and vertebrates, with many more mutants being continually engineered from their wild forms. The array of opsins now available gives experimentalists a wide range of characteristics to choose from (e.g. ion selectivity, kinetics, spectral sensitivity) which must be carefully matched to the target cell of interest. To facilitate their application, we are developing a database of models, parameterised by fitting them to patch-clamp recordings using the algorithms of PyRhO (Evans et al. 2016). Without the need for collecting data, these models can then be inserted into cellular or network models of interest to prototype experiments and assess the opsin's suitability for the target system. We describe the minimal set of experimental data required to characterise these existing three-, four- and six-state models, for variations in flux and membrane voltage, along with the requirements for optional extensions including temperature, wavelength and pH. We present some fitting results for popular opsins such as Channelrhodopsin2 (ChR2) with additional pseudo-variables describing their kinetics for easy comparison, summarised by activation, deactivation and off time constants. Finally, plans are outlined for further developing the PyRhO web portal Prometheus (Evans & Nikolic, 2016) to allow data to be uploaded for fitting and parameter sets to be contributed. In this way, we hope that the database will be a community driven resource for computational and experimental neuroscientists, using and contributing to a wide range of prêt-à-porter models for in silico experiments.

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Poster number: P-M166
Theme: Methods and techniques

"Hopefully not all in vein" - exploring neurochemical and BOLD responses to negative stimuli in the human amygdala

Authors: Charlotte Horne, Dr Ray Norbury - *Psychology University of Roehampton*

Background: The human amygdala has long been a target for functional Magnetic Resonance Imaging (fMRI) studies because of its involvement in emotional processing. However, amygdala BOLD may be confounded by stimulus correlated signal from local draining veins (e.g. Basal Vein of Rosenthal). Here we used functional Magnetic Resonance Spectroscopy (FMRS) to assay right amygdala glutamate in combination with an amygdala activation task.

Methods: Seventeen healthy participants underwent whole brain fMRI and fMRS (voxel dimensions: 1.5 x 1.5 x 1.5 cm, placed over the right amygdala) in a single session. During scanning, participants completed a simple ABABA block design experiment. Baseline blocks (A) consisted of triplets of geometric shapes alternating with triplets of threatening scenes/negative facial expressions (B). Response latency and accuracy were recorded. Functional MRI data were pre-processed and analysed using FSL v5.0.1, fMRS data were pre-processed using the Matlab-based FID-A toolbox (Simpson, 2015) and subsequently analysed using LC Model (Provencher, 1993).

Results: Right amygdala BOLD response to threatening images/negative facial expressions was significantly increased as compared to baseline (z = 6.73, x 20, y -6, z -12, cluster size = 67 voxels, p = 1.34e-11). In addition, right amygdala glutamate was significantly increased relative to baseline (dependent samples t-test, t(16) = 3.76, p = 0.002).

Conclusions: Consistent with previous studies we observed significantly increased BOLD response to negative stimuli. We also observed a significant increase (~15%) in right amygdala glutamate levels during active vs. rest blocks. Amygdala metabolite concentration changes and BOLD signal are both strongly related to neuronal activity. The latter, however, may be confounded by stimulus correlated signal from local draining veins. Here, we demonstrate the utility of fMRS to measure metabolite changes in the human amygdala which may prove to be a useful additional metric when investigating the function of this structure.

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Poster number: P-M167
Theme: Methods and techniques

Functional neurochemistry and BOLD-fMRI in the human brain acquired at 7 Tesla

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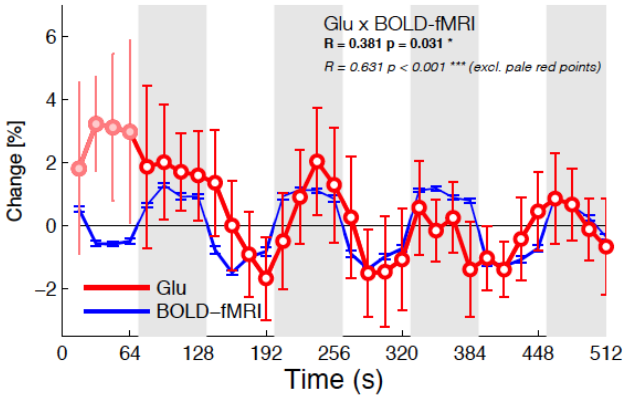
BACKGROUND
The blood-oxygenation level dependent (BOLD)-fMRI response is one of the most widely used measures of human brain activity yet is not a direct measure of action potentials, or synaptic activity. 1H-MRS is a non-invasive measure of absolute concentrations of neurochemicals. 1H –MRS, particularly in the absence of any sensory stimulation, has been exploited to identify biomarkers of normal and pathological brain states. While several recent studies have measured functional 1H-MRS during specific tasks, no study to date has quantified simultaneous changes in neurochemicals and brain activity using BOLD-fMRI. Here, we reveal a specific relationship between changes in BOLD-fMRI and glutamate at time scales relevant to conventional fMRI block design experiments (64s).

RESULTS
We developed and implemented a novel functional MR-sequence that simultaneously recorded BOLD-fMRI and 1H-MRS (combined fMRI-MRS) in the human visual cortex. We acquired combined fMRI-MRS data in the same time volume at 7T. Participants viewed 64-sec stimulus blocks of a flickering checkerboard alternating with a blank black screen. Absolute glutamate concentrations increased by 0.15 ± 0.05 µmol/g (p = 0.011) during stimulation, equivalent to an increase of 1.92 ± 0.66% from the baseline concentration. We also found a significant correlation between glutamate and BOLD-fMRI time courses (r(31) = 0.381, p = 0.031) on the group level. Control measures show that these changes cannot be explained either by spectral line-narrowing during BOLD-changes or resting state variations in glutamate.

DISCUSSION

In summary, we tested the feasibility of a novel combined fMRI-MRS method by measuring responses to a flashing checkerboard in the human visual cortex. Our results demonstrate a strong link between BOLD-responses and glutamate: (i) average BOLD and glutamate changes increased during stimulation and (ii) glutamate and BOLD-fMRI signals correlated significantly over time. Importantly, we show that the relationship between the glutamate and BOLD-response is specific to the activated visual cortex, and absent in the resting visual cortex.

Glutamate time course correlated with the BOLD-fMRI response.

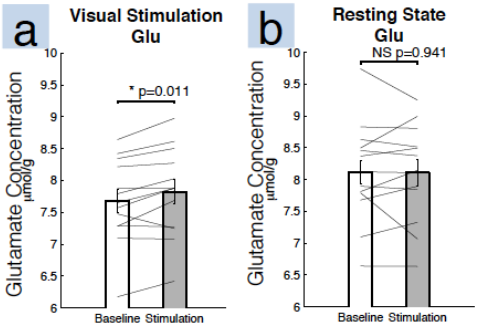


Δ Glutamate = $((G_i - G_{baseline}) / G_{baseline}) * 100$

Each glutamate time point is the average of 4 spectra. Data were normalized, concatenated, smoothed and averaged across subjects (N=13, ± s.e.m.). R = Pearson's Correlation Coefficient, p = *p*-value.

Glutamate increased significantly during stimulation periods (1.92 ± 0.66 %) .

When the same analysis steps in (a) were applied to resting state data, where participants had their eyes shut and no stimulation was delivered, no glutamate increases were observed (b).



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Poster number: P-M168
Theme: Methods and techniques

Finer parcellation reveals intricate correlational structure of steady-state fMRI signals

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Anatomical and functional parcellations of the human brain are widely used, for example, 'automated anatomical labelling' into 90 cortical and subcortical regions ('AAL90', Tzourio-Mazoyer et al., 2002), spatially constrained clustering of functional correlations ('C400', Cradock et al., 2013), or multi-modal parcellation from the Human Connectome Project ('HPC360', Glasser et al., 2016). However, only a modest amount of correlational information can be retrieved at these comparatively coarse resolutions (and only about half of the pairwise functional correlations between resting-state signals are consistently significant).

We propose a finer parcellation ('M758') which increases the bivariate mutual information retrieved by functional correlations approximately 100-fold (and the multivariate mutual information approximately 10-fold). Subdividing each AAL area separately on the basis of local functional correlations, we define 758 highly inter-correlated and spatially largely contiguous volumes ('functional clusters'). At this finer resolution, a large majority of pairwise functional correlations is consistently significant (86% with $p<.01$, $cv<1.0$).

Moreover, fibre tracking reveals consistent anatomical connectivity between these 'functional clusters', echoing the global pattern of functional correlations. In fact, even local patterns of cluster-to-cluster correlations often mirror cluster-to-cluster connectivity in

detail and with high significance (p<.00001). The global and local correspondence of functional correlations and anatomical connectivity at the level of 'functional clusters' further validates the proposed parcellation.

We conclude that a finer parcellation, which combines both anatomical and functional criteria, unlocks a treasure trove of intricate correlational structure in resting-state BOLD signals.

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Poster number: P-M169
Theme: Methods and techniques

Differentiating features of white matter damage following traumatic brain injury

Authors: Niall Bourke, Maria Yanez-Lopez, James Cole, Peter Lally, Peter Jenkins, Sara De Simoni, David Sharp - *Medicine Imperial College London*

Introduction

Multi-shell diffusion MRI allows exploration of white matter tracts using the Neurite Orientation Dispersion and Density Imaging (NODDI). White matter damage is commonly seen following traumatic brain injury (TBI) and results from diffuse axonal injury. Here we investigate the relationships between FA and NODDI metrics after moderate-severe brain injury, as well as exploring how diffusion measures relate to atrophy and cognitive impairment.

Methods

Thirty patients with moderate-severe TBI (26 male, mean age=38.5±10.1) and 21 age-matched controls (16 male, mean age=38±10.5) had high-resolution T1 and multi-shell diffusion imaging (b1=700, b2=2000 s/mm2). Analyses of DTI metrics FA, MD, RD were compared with neurite density (ND) and orientation dispersion (OD) and isotropic volume fraction (ISOVF; free water) from the NODDI model. These results were investigated in relation to atrophy and cognitive impairment.

Results

Widespread reductions of FA were seen in patients following TBI, as expected (Fig. 1). Extensive abnormalities in ND, OD and ISOVF were also observed, although these affected less numerous white matter tracts than FA (Fig.1). Distinct patterns of NODDI abnormalities were observed. For example, widespread FA, OD and ISOVF abnormalities were seen in the corpus callosum, but ND abnormality was only observed in the splenium. Decreased neurite density was significantly associated with decreased processing speed and worsening working memory retention. A similar relationship was also observed for FA, although the relationship was observed in a smaller number of voxels, principally within the corticospinal tract.

Conclusion

The results show that abnormalities in FA after TBI can be decomposed into non-spatially overlapping changes in neurite density and orientation dispersion. These measures provide an estimate of the impact of TBI on the density of axons in the white matter (ND) and their orientation (OD). Therefore, the measures potentially provide a more precise estimate of the underlying neuropathology seen after TBI. Importantly, the results are not explained by the presence of white matter atrophy. In addition, ND is strongly related to the degree of cognitive impairment, and this may be a more sensitive measure than FA.

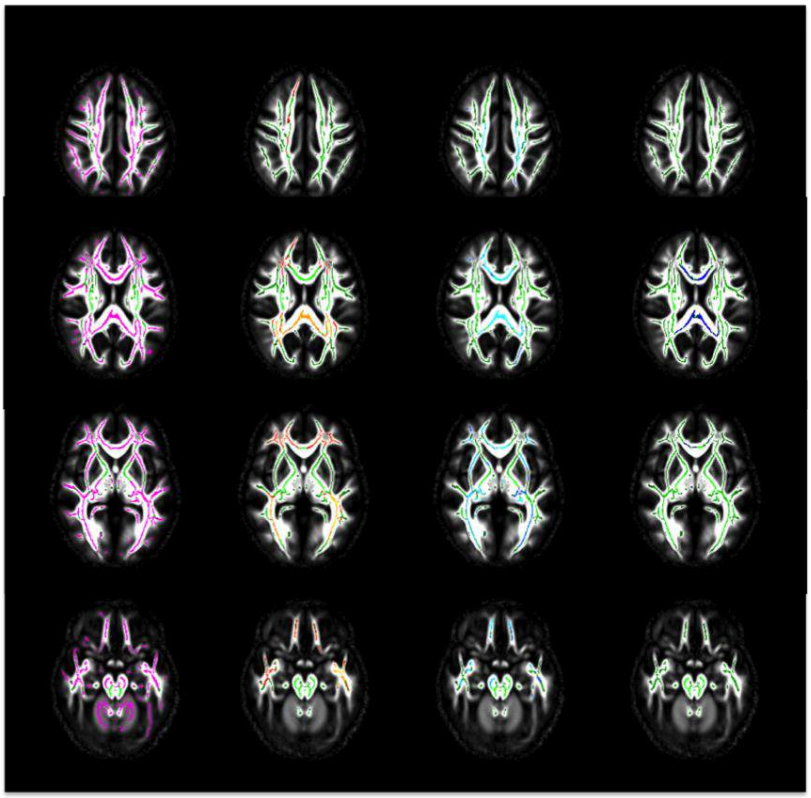

Figure 1. Axial slices of whole brain TBSS skeletonised contrasts between traumatic brain injury patients and controls, adjusting for age, gender and intracranial volume (TFCE: p<0.05). Pink: Fractional Anisotropy reduced in patients, Red-yellow: Neurite density reduced in patients, Light blue: Orientation dispersion increased in patients, Dark blue: Isotropic (free-water) volume fraction increased in patients.

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Poster number: P-M170
Theme: Methods and techniques

Establishing sex-specific in vitro models of ischemic cell death

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The differences between men and women in relation to stroke risk and pathological outcome are well recognized and the mechanisms underlying any sex differences in injury mechanisms warrant investigation. Experimental models to study cell death include cell-specific cultures (e.g. neuronal), region-specific cultures (e.g. organotypic hippocampal sliced cultures) and ex vivo (intact) brain slices. In the current study we developed sex-specific ischemic models using brain slices and organotypic hippocampal sliced cultures (OHSCs) to determine the feasibility of such models for examining sex-specific differences in cell death. We used an ex vivo brain slice model whereby slices were exposed to oxygen and glucose deprivation (OGD) in order to mimic ischemia and stained with 2, 3, 5-triphenyltetrazolium chloride (TTC) to visualise (and measure) the ischemic area of cell death. In adult brain slices there appeared to be a sex difference in the amount of cell death with male-derived slices showing significantly more cell death than female-derived slices. We then developed a sex-specific model of OHSCs which were also exposed to OGD in order to mimic ischemia. We successfully prepared, and were able to maintain, OHSCs from pups at postnatal P6-9 days which were sexed prior to the OHSCs being prepared. We optimized the experimental parameters in order to maintain the OHSCs and produce an adequate amount of cell death to allow either increases or decreases to be detected. There was a significant ($P < .0001$) reduction in the amount of cell death in female-derived OHSCs compared to male-derived OHSCs following 4 hours exposure of OGD. Thus, we have developed two sex-specific models of in vitro ischemia which both show a female protection in terms of the amount of cell death produced. Such models will be useful in examining the mechanisms underlying these sex-specific differences in cell death following injury.

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Poster number: P-M171
Theme: Methods and techniques

An alternative view on tACS: Is it an effective tool for cognitive research?

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Transcranial alternating current stimulation (tACS) may shed light on the relationships between oscillatory activity and cognitive processes and so has been widely used to entrain or modulate brain oscillations in experimental settings. Brain oscillations show highly dynamic behaviour during cognitive tasks. For example, beta oscillations decrease in power within a couple of milliseconds during memory processing followed by a subsequent increase in amplitude. If tACS can be shown to influence brain oscillatory behaviour in a similar time range it would be useful for answering causal questions about these dynamics. In a series of experiments we addressed the question of whether event-related, transient tACS in the beta frequency range can be used to modulate 2 different processes: episodic memory formation and motor cortex excitability. Experiments 1 and 2 sought to replicate and extend findings from a recently published rTMS study. 72 healthy human participants engaged in an incidental encoding task of verbal and non-verbal stimuli while receiving tACS to the left and right inferior frontal gyrus (IFG) at 6.8Hz, 10.7Hz, 18.5Hz, 30Hz, 48Hz and sham stimulation for 2s during stimulus presentation. Experiment 3 addressed the question whether 10s of beta tACS can be used to entrain brain oscillations in the primary motor cortex (M1). By administering tACS to M1 at the individual motor beta frequency of 8 subjects, we investigated the relationship between the size of TMS induced MEPs and tACS phase. In experiments 1 and 2 beta tACS did not affect memory performance. Likewise, no entrainment effects were found in experiment 3. MEP size was not modulated by tACS phase, indicating that this stimulation protocol does not entrain beta oscillations in M1. Taken together, these findings suggest that event-related short duration tACS may not effectively modulate brain oscillations.

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