Poster number: P-T001
Theme: Attention, motivation, behaviour

Dopamine and motivational effects on patch leaving behaviour in humans

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Foraging models of behaviour provide an ecological framework in which to understand cost benefit decision making, while disruption of these systems may underlie common neurobehavioural disorders such as apathy (loss of motivation). When to leave a location (patch) in which returns are diminishing over time to travel to a new one (at the expense of time and effort) is a crucial foraging decision. Numerous studies have found animal patch leaving behaviour conforms to the predictions of Marginal value theorem (MVT) – a framework that provides an optimal characterisation of factors that influence this decision. Humans must also make similar decisions, but what factors drive such behaviours, and the neurobiological substrates of these decisions are poorly understood. A separate literature suggests the neurotransmitter dopamine may play a crucial role in signalling background environmental reward rates, whilst it is also strongly linked to invigorating and maintaining behaviour towards goals.

We have developed a patch leaving task, and used it to test whether human decisions conform to MVT principles. Testing the same task in 40 patients with Parkinson's disease – a common neurodegenerative condition in which apathy commonly occurs and a primary dopaminergic deficit is the defining feature– on and off their normal dopaminergic medications, we examined the role of dopamine in tracking background reward variables, and the effect of disrupted underlying motivational state.

Results demonstrate that patch leaving decisions in healthy subjects are influenced by factors incorporated within MVT, but that variability in such decision making relates to individual differences in self-report measures of motivation (apathy). Dopamine levels significantly altered the influence of the background reward environment on foraging decisions, an effect that was modulated by motivational state.

Overall we show that human patch leaving decisions conform to MVT principles and may be linked to the function of the dopaminergic system. Studying them more closely may provide a framework for understanding variability in motivation in health and disease.

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Poster number: P-T002
Theme: Attention, motivation, behaviour

Putting attention in the spotlight: The influence of APOE genotype on visual search in mid-adulthood

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Background: The Apolipoprotein E (APOE) e4 allele is associated with greater decline in cognition with age, yet effects of this gene are also observed earlier in the lifespan. This research selectively explores genotype differences in the allocation of visuospatial attention in mid-adulthood.

Method: 66 volunteers, aged 45-55 years, completed two complementary paradigms probing the active selection of information at the focus of attention (a dynamic scaling task) and the role of perceptual capacity differences. Performance differences were compared across APOE genotype groups (e2, e3, e4).

Results: Performance of the e4 carriers did not significantly differ from the homozygous e3 group on either the dynamic scaling task or perceptual load task. E2 carriers, however, were slower to detect targets on the dynamic scaling task, with this group showing poorer performance at larger cue size.

Conclusions: The lack of an e4 difference in visuospatial attention, despite previous suggestion in the literature of genotype effects, indicates that select attentional processes are maintained in e4 carriers in mid-adulthood. The association of e2 genotype with less efficient visual search complicates the premised protective effects of this allele on cognitive ageing.

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Poster number: P-T003
Theme: Attention, motivation, behaviour

The Cuttle Shuttle: Prediction of Prey Behavior by Cuttlefish

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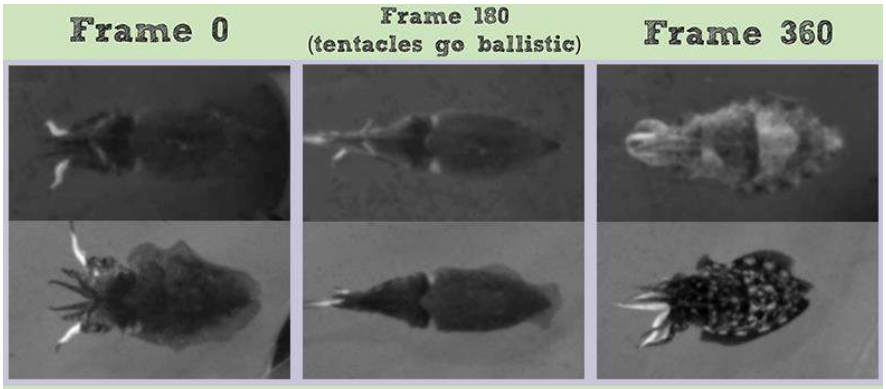
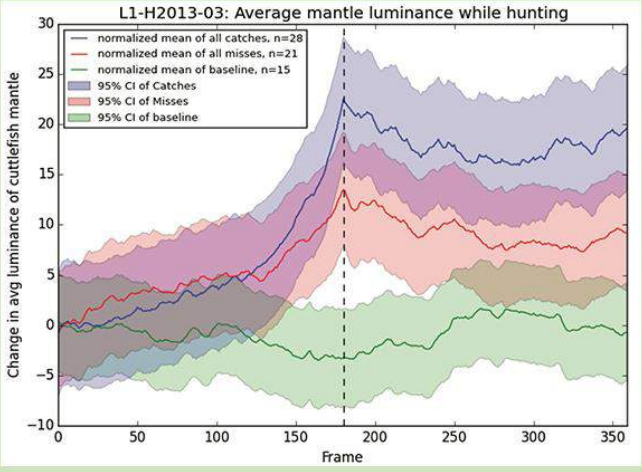
Cuttlefish actively control their body color, texture, and shape (collectively called their "body pattern"). The Cuttle Shuttle examined predictive model-making behavior by asking cuttlefish (Sepia officinalis) to hunt prey that moved with ever-increasing complexity. Because cuttlefish use active camouflage (their body pattern is rapidly and directly controlled by their nervous system) this species presents the possibility of directly observing the state of a nervous system non-invasively. Tools and methods prototyped in rats by the Kampff Lab were translated into an assay appropriate for cuttlefish, the design of which was informed by both field and lab work done by the Marine Biology Lab at Woods Hole, USA. In this experiment, cuttlefish hunted for their food 4 days out of 7 while being video recorded; their prey was a piece of shrimp at the end of an arduino-controlled skewer. We observed body pattern sequences in five 15-month-old sexually immature cuttlefish (Sepia officinalis) which do not clearly categorize as camouflage or communication. Our quantitative analyses thus far measures mantle luminance and spatial frequency while the cuttlefish makes a tentacle shot. These initial measurements, along with qualitative syntheses of our video footage, suggest that cuttlefish body patterns can be treated as an observable correlate of the animal's current model of the world, encompassing its expectations and the knowledge it has constructed thus far. We are therefore encouraged to translate infant cognition experiments into assays appropriate for cuttlefish, as treating the body pattern as a "read-out" of neural activity gives us more flexibility when studying complex behaviors that require environmental enrichment and freedom of movement in ways not allowed for by common head-fixing or neural recording mechanisms. In order to compare cuttlefish and human infants, we will next collaborate with the Brighton Sea Life Center and Sussex University to design learning games for cuttlefish, during which we will explore what a "surprised" cuttlefish looks like and how it behaves in the presence of novelty.





Top: Ethogram showing the first and last catches made by one animal (L1-H2013-03). The middle column shows the instances when this cuttlefish's tentacles go ballistic; the left and right columns show frames exactly 3 seconds before and after TGB, respectively. The videos used to generate these ethograms can be found at http://bit.ly/2cvkE5b. **Left:** Plot showing average luminance of cuttlefish mantle and head as it shoots its tentacles (resulting in either a catch or a miss) or during "baseline". The "baseline" sequence consisted of the 6 seconds before the prey entered the water, centered around the moment when a cue LED turns on above the water's surface. The dotted vertical line indicates the moment tentacles go ballistic, or for baseline, the moment when the LED turns on.

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Poster number: P-T004
Theme: Attention, motivation, behaviour

Molecular diversity of GABA neurons in the ventral tegmental area and substantia nigra

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Midbrain dopamine neurons of the ventral tegmental area (VTA) and substantia nigra (SNC) are central to controlling voluntary movement, working memory, motivation and reward processing, as well as being implicated in multiple neuropsychiatric disorders. Dopamine neuron activity is strongly regulated by GABA neurons, including those found in the VTA and SNC, which make up around 30% of the neuronal population. Little is known about the functional roles of GABA neurons in this system and in particular whether there are functionally-distinct subgroups. Indeed, GABAergic neurons in other regions, including the hippocampus, cortex and spinal cord, exhibit considerable molecular, anatomical and functional diversity. We, therefore, hypothesized that GABA neurons in the VTA and SNC are also likely to exhibit similar levels of diversity. As a first step, we are seeking to uncover molecular markers that identify distinct GABAergic subpopulations.

To do this, we are taking two complimentary approaches. First, we are taking a biased approach by investigating the expression of molecular markers known to identify GABAergic subgroups in other regions (e.g., hippocampus) using immunostaining. For example, we find that nNOS is selectively expressed in a subset of GABA neurons in the VTA. Using NOS1Cre transgenic mice and stereotaxic injections of an AAV expressing ChR2-mcherry (cre-dependant) into the VTA, we have traced the projections of these nNOS expressing neurons. We found that nNOS+ neurons in the rostral linear nucleus sends long range projections, whereas nNOS+ neurons in the parabrachial pigmented area may be interneurons.

Second, we are taking an unbiased approach, using tagged ribosomal affinity purification to isolate RNA specifically from GABA neurons and dopamine neurons in the ventral midbrain for RNA sequencing. By directly comparing these two transcriptomes, we have identified a number of potential candidate molecular markers of subpopulations of GABA neurons. Identification of these molecular markers will allow for the future, selective targeting and manipulation of subpopulations of GABA neurons in the VTA and SNC and thus a clearer understanding of the role of these diverse GABA neuron groups within the midbrain dopamine system.

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Poster number: P-T005
Theme: Attention, motivation, behaviour

Exploring a Distinct Role for Dorsal Raphe Dopamine Neurons in Social Motivation

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The motivation to establish and maintain social connections is essential for a social species to develop and thrive. This motivation may arise from the rewarding value of social interactions or the need to avoid situations of isolation or loneliness. We recently identified a functional role for dopamine neurons in the dorsal raphe nucleus (DRN) in representing the subjective experience of social isolation and providing the motivational drive to re-establish social contact. Using ex vivo electrophysiology in mice, we showed that 24 hours of social isolation induces robust synaptic potentiation at glutamatergic synapses onto these neurons. In vivo calcium imaging further revealed that DRN dopamine neurons show increased activity upon social contact following isolation. In freely-behaving animals, ChR2-mediated optogenetic activation of DRN dopamine neurons recapitulated a 'loneliness-like' state, in which mice displayed an increase in social preference, but (in the absence of social contact) avoided stimulation, suggesting a negative affective state. Conversely, in mice socially isolated for 24 hours, NpHR-mediated optical inhibition of DRN dopamine neurons prevented the rebound increase in sociability typically observed after a period of isolation. Interestingly, the magnitude of these effects was predicted by social rank, with dominant mice showing greater sensitivity to changes in DRN dopamine activity. We are continuing to tease apart the functional role of different downstream projections of these dopamine neurons, which densely innervate the bed nucleus of the stria terminals (BNST) and Central Amygdala (CeA). In addition, we are exploring the relationship between activity in the DRN dopamine neurons and social hierarchy, and how the naturally-occurring activity within this population is modulated by motivational state.

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Poster number: P-T006
Theme: Attention, motivation, behaviour

Cannabinoid modulation of electrically evoked dopamine release in rat brain slices

Authors: Kate Peters, Jacqueline-Marie Ferdinand, Andrew Young - *Neuroscience, Psychology and Behaviour University of Leicester*

Evidence suggests a link between cannabis and schizophrenia. Cannabis exacerbates symptoms in patients and can precipitate psychosis in vulnerable individuals. Furthermore, cannabinoid agonists can induce psychotic symptoms in those without schizophrenia. A primary action of cannabis is via endogenous cannabinoid 1 (CB1) receptors. Cannabinoids can modulate dopamine (DA) release in the mesolimbic pathway and have actions in local circuits within nucleus accumbens (NAc).

Short-term chronic (subchronic) blockade of NMDA-type glutamate receptors using phencyclidine (PCP) causes robust and prolonged deficits in cognition, and has been proposed as a model for specific deficits seen in schizophrenia. The present study aimed to assess the modulatory effects of a CB1 receptor agonist on electrically evoked DA release in NAc of rat brain slices in vitro, and to investigate the effect of subchronic pretreatment with PCP, modelling changes seen in schizophrenia.

Using fast scan cyclic voltammetry (FSCV), DA was measured at carbon fibre electrodes placed in the NAc shell of coronal brain slices (400µm) cut from juvenile female Wistar rat brains. Slices were continuously superfused with oxygenated cerebrospinal fluid and a carbon fibre electrode was placed in the NAc shell. Voltammetric scans (-0.4V to +1.3V to -0.4V; 400V/sec) were applied and DA was measured as the background subtracted current at 600mV. Twelve trains of electrical stimulations (30 pulses; 60Hz; 300µA; 4ms) were applied at 3 min intervals. After baseline recording of 4 electrical stimulations drugs were applied in the next 4 stimulations. Finally 4 stimulations were delivered without the drug to allow for washout (total stimulations 12).

In control slices the CB1 agonist arachidonylcyclopropylamideon (ACPA) produced a sustained increase in stimulated DA release independent of dose (0.1, 1, 10µM). After PCP, the ACPA effect on DA was potentiated. Furthermore, in contrast to control slices, in slices from PCP treated animals, ACPA produced a dose-dependent increase in evoked DA release.

This modulation of DA release by CB1 agonists, and the enhancement after PCP pretreatment, may have implications for enhancing our understanding of the effects of cannabis in schizophrenia.

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Poster number: P-T007
Theme: Attention, motivation, behaviour

How does the brain encode distinct values? Electrophysiological evidence for the common currency hypothesis

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Social decision-making is the most complex cognitive function performed by the human brain (Seo & Lee, 2012) but there is little research on the temporal mechanisms of decision-making. The current study examined the temporal properties of preference choices in social and non-social domains using event-related potentials (ERP). Participants (N = 24) made attractiveness choices between pairs of faces or landscapes (each pair depicted one happy and one sad image). Results indicate that the amplitudes of the N1, N2 and early late positive potential (LPP) components were modulated by stimuli type. N1 and N2 were found to have enhanced activation for social stimuli (faces) compared to non-social (landscapes), indicating that early ERP components are sensitive to the properties of social stimuli. Whereas, the early LPP component (400-600 ms) was strongly sensitive to non-social stimuli than social, illustrating a distinctive allocation of attentional and motivational resources to non-social stimuli. Finally, during the later LPP (600-800 ms) findings suggest that there is a temporal overlap in the mechanism that processes social and non-social preference judgements. The results indicate that although initially there are temporal differences in the neural mechanisms supporting the “social-specific” hypothesis, during the later processing stages there is an overlap in temporal activity suggesting a common mechanism by which participants make choices, supporting the “common currency” hypothesis.

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Poster number: P-T008
Theme: Attention, motivation, behaviour

Evidence for human ghrelin GHS-R1a and orexin OX1 heteroreceptor complex formation in a heterologous system

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Ghrelin and orexin are two peptides implicated in the regulation of energy balance and modulation of food-related motivation at the level of the midbrain dopamine reward system. Their actions are mediated by G-protein coupled receptors (GPCRs): ghrelin 1a and 1b (GHS-R1a, GHS-R1b) for ghrelin and orexin 1 and 2 (OX1, OX2) for orexin. The ghrelin 1a (GHS-R1a) and orexin 1 (OX1) receptors are expressed broadly in the brain, particularly in the hypothalamus, an important feeding center. The relation between peptides in the hypothalamic arcuate nucleus and the ventral tegmental area (VTA), the major area in the mesolimbic dopaminergic system, has been described but the modulation at the level of receptors remains unclear.

Traditional approaches to know the mechanism of neurotransmission of dopaminergic neurons in the mesolimbic system have focused on targeting neuronal receptors as single entities. From the discovery that GPCRs for neuromodulators may form heteroreceptor complexes, our hypothesis is that ghrelin and orexin receptors may interact and form novel functional units that may specifically participate in the central regulation of food intake and energy balance. As a proof of concept we have investigated the potential of human GHS-R1a and OX1 receptors to form heterocomplexes.

Formation of GHS-R1a -OX1 receptor heteromers in transfected HEK293T cells was detected by Bioluminescence Resonance Energy Transfer (BRET) and Proximity Ligation (PLA) assays. Furthermore, a negative crosstalk was identified in cells co-expressing both receptors by assessing mitogen-activated protein kinase (MAPK) pathway, calcium signaling and by a label-free dynamic mass redistribution assay.

Ghrelin and orexin peptides stimulate food intake and modulate motivation of feed. GHS-R1a and OX1 receptors are expressed in feeding centers and constitute potential pharmacological targets for treating obesity and substance use disorders. Experiments in sources endogenously expressing GHS-R1a and OX1 receptors are needed to know the functional relevance of the heteromer. From the negative crosstalk here identified, it is tempting to speculate that GHS-R1a-OX1 receptor heteromers are important players in mediating the response to the combination of different orexigenic signals.

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Poster number: P-T009
Theme: Attention, motivation, behaviour

Tracking emotions in the brain – Revisiting the Empathic Accuracy Task

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Introduction: Empathic accuracy (EA) describes how accurately individuals can infer other people's emotions and as such is a crucial component of successful social interaction. Brain areas associated with mentalising have also been implicated in EA. In this study, we set out to further examine the neural bases of EA using a modified paradigm and novel stimuli to study the dynamic processes involved in tracking other's emotional states and changes in emotional intensity.

Methods: In an fMRI study, 34 healthy participants (15 males) watched four newly acquired video clips of targets (one female and one male) talking about an emotional event from their past (two happy and two sad) and two neutral videos. Participants continuously rated the target's emotional intensity using a button box. EA scores were obtained by correlating these ratings with the target's own ratings throughout the clips. Participants were also asked to identify the main emotion depicted and rate their own emotional states for each clip (as a measure of affective empathy).

Results: Participants showed high EA scores across clips (mean r = .75, SD = .07). Furthermore, they showed high levels of affective empathy with affect sharing for 70% of the clips. Relative to neutral clips, the bilateral superior temporal cortex, temporal poles, inferior frontal gyri and supplementary motor area were more highly activated when watching emotional clips (p<.05, family-wise error correction). Moreover, during the video clips, activity of the same regions varied dynamically along with the targets' self-rated emotional intensity as well as the participants' ratings.

Discussion: To our knowledge, these data are the first to show that brain areas previously associated with mentalising and empathy are involved in tracking dynamic changes in other's emotional intensity. Our novel neutral control condition enabled us to show that these brain changes are specifically related to emotion processing. Furthermore, the fact that we observed high levels of EA and affect sharing shows that this task successfully recruits both cognitive and affective components of empathy. This task provides a naturalistic way of assessing empathy on a moment-to-moment basis as well as the opportunity to study EA for distinct emotions.

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Poster number: P-T010
Theme: Attention, motivation, behaviour

Shared functional neuroanatomical correlates of executive control in multitasking and working memory

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Introduction: Empathic accuracy (EA) describes how accurately individuals can infer other people's emotions and as such is a crucial component of successful social interaction. Brain areas associated with mentalising have also been implicated in EA. In this study, we set out to further examine the neural bases of EA using a modified paradigm and novel stimuli to study the dynamic processes involved in tracking other's emotional states and changes in emotional intensity.

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Poster number: P-T011
Theme: Attention, motivation, behaviour

Competing drives of hunger and sleep on performance in sleep-restricted rats

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Studies assessing the impact of sleep restriction on attention and cognitive performance in rodents often combine functional – behavioural measures with electroencephalographic (EEG) measures of vigilance. Such behavioural tasks commonly utilize food reward to motivate performance, yet it is unclear whether the differing biological drives of hunger and sleep interact to modulate outcome in such studies.

The effects of feeding status was compared (i.e., ad libitum vs. food restricted (>85% of free feeding weight)) on two appetitive behavioural tasks in sleep-restricted male Sprague-Dawley rats. One cohort was trained on a psychomotor vigilance task (PVT), responding to an imperative cue (i.e., magazine light) following a preparatory cue (i.e., house-light) to gain a food reward. Trial completion, number of omissions and response latencies were measured. Rats performing the PVT were also surgically implanted to record the EEG. A second cohort trained to press a lever for food reward under a progressive ratio (PR) schedule, with breakpoint as a primary measure (i.e., the press component at which a subject stops responding). Both cohorts underwent a previously validated 11-h sleep restriction protocol (McCarthy, Loomis et al. 2016) before performance was assessed.
Analyses of the EEG recordings confirmed that rats fed ad libitum and the food-controlled group underwent a similar amount of sleep loss during sleep restriction. PVT testing revealed significant impairments in ad libitum-fed rats, while food-controlled rats showed no deficits. Ad libitum-fed rats completed significantly less trials, made more omissions and had longer response latencies. EEG analyses showed that ad libitum-fed rats obtained more sleep during the task than food-controlled rats. In contrast, for the PR test breakpoint remained unchanged following sleep restriction for both feeding regimes, although it was significantly higher in the food-controlled group at baseline.
In conclusion, the present study cautions that while sleep restriction does not differentially alter motivation for food reward in rats, hunger drive will negate the effects of sleep restriction on appetitive task performance.

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Poster number: P-T012
Theme: Attention, motivation, behaviour

Characterising the nature of proactive and reaction inhibition in a task of selective stopping: A TMS study

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Introduction
Behavioural inhibition is subdivided into reactive (RI) and proactive inhibition (PI), the former becoming active using external cues and the latter an ingrained type of inhibition, serving to facilitate reactive stopping. Recent studies applying Transcranial magnetic stimulation (TMS) in different directions and with specific pulse widths have shown that different inputs into the motor cortex (M1) are differentially modulated depending on behavioural demands. The functional role of these different inputs into M1 with respect to mechanisms of behavioural stopping has not yet been elucidated.

Methods
We employed TMS during the conditional stop signal task to probe RI and PI in 15 healthy individuals. TMS was applied in two ways: a postero-anterior direction and antero-posterior with 120µs and 30µs pulse widths respectively (PA-120/AP-30). These parameters have been shown to selectively recruit the aforementioned inputs into M1. TMS was applied at different phases of the go (preparation to stop) and stop processes and MEPs recorded from the right FDI muscle, to reflect PI and RI respectively.

Results
During the go trials (PI), PA and AP MEPs were differentially modulated: AP inputs were reduced when PI was implemented, whereas PA inputs were enhanced. This difference reached statistical significance ($p=0.039$, $t=2.404$). For RI we found that stopping the left hand inhibited MEPs more than when the right hand was stopped, for both PA and AP inputs. However, this was statistically significant for PA MEPs only ($p=0.007$, $t=3.319$). Interestingly, PA MEPs during successful stopping were significantly higher than those at baseline ($p<0.001$, $t=10.857$, 95% CI = 1.01-1.50).

Discussion
AP and PA inputs into M1 are differentially modulated by behavioural inhibition: preparation to stop specifically inhibits AP inputs whereas stopping is mediated predominantly by PA inputs. We also have an insight into the nature of behavioral inhibition: stopping the left hand induces a global inhibition, which is more prominent than when the right hand is stopped (selective inhibition). Furthermore, we propose that the PA inputs post-stopping may reflect a remnant of the GO process, despite successful stopping.

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Poster number: P-T013
Theme: Sensory & motor systems

Itchy & Scratchy: Are A-fibres necessary for scratching an itch to feel good?

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The study aims to further explore the somatosensory mechanisms of (experimentally induced) itch, and scratching in humans; using microneurography, psychophysics and a case-study with a rare neuronopathy patient, IW, (absence of A-beta nerve fibres, intact C-fibre function). It is well established that itch itself is driven primarily by C-fibres, but the mechanisms driving scratching behaviour, and the associated reward, are unknown.

Two distinct itch induction pathways have previously been described; Histamine mediated itch, via H1 receptors on mechano-insensitve C-nociceptors, and cowhage (mucuna pruriens) mediated itch, via PAR2 receptors on mechanosensitive polymodal C-nociceptors. Spontaneous activity of mechano-insensitive C-nociceptors has previously been reported in microneurography experiments on patients with chronic pruritus.

In the current study we present single-unit microneurography recordings of the prolonged responses to the application of Cowhage spicules (mucuna pruriens) within the receptive fields of mechanosensitive C-nociceptors in healthy control subjects, paired with subjective measurements of itch quality.

In an attempt to identify the contribution of somatosensory afferents to the reward associated with scratching an itch, quantitative psychophysical testing was carried out in a control population in response to cowhage & histamine induced itch on the forearms, and compared to data obtained from IW. As expected, control subjects rated scratching an itch as pleasant (sig. mean increase: +3.0); A similar pleasant response to scratching an itch is seen in IW – despite the lack of A-beta afferents.

Results will be discussed in terms of the contribution of C-fibres, as opposed to A-fibres, driving the reward of scratching an itch, and therefore providing a potential mechanism to interrupt the itch/scratch cycle in chronic itch.

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Poster number: P-T014
Theme: Sensory & motor systems

Off-line improvements in motor skill depend on amount of practice, not explicit sequence knowledge or time: an argument against wakeful consolidation

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Skill levels on some motor tasks have been shown to spontaneously improve between practice sessions, a phenomenon known as consolidation. Consolidation on motor tasks which contain an explicit declarative component has been shown to be dependent on sleep; whereas similar tasks which rely only on implicit learning, without the declarative component, can show consolidation across wakefulness (Robertson et al., 2004). The serial reaction time task (SRTT), where participants learn a sequence of button presses distributed among random presses, shows this dissociation. However, in the many studies that use this paradigm, in order to achieve equivalent levels of skill across explicit and implicit learning, the amount of practice differs between the two conditions, with the implicit condition typically receiving around 40% more sequence repetitions than the explicit condition in both the initial training session and at later follow-up.

Here, we investigated whether wakeful consolidation could be demonstrated in the explicit SRTT if the amount of practice, rather than skill level, was matched with that used in the implicit condition. We tested 60 right-handed participants on one of 4 conditions of the SRTT: the original implicit and explicit conditions, as well as an explicit condition that was matched with the implicit condition for overall practice, and another that was matched for practice only in the evening session.

While we replicated the finding of a difference between consolidation on the original implicit and explicit SRTT conditions, we showed that controlling for amount of practice, specifically in the follow-up session, eliminates any difference. We also performed a curve fitting analysis to show that participants' improvement in response time to the sequence in the evening session could be accounted for by a continuation of the same learning process which was active in the morning session, rather than by a an additional consolidation process.

Our results provide an alternative explanation for differences in wakeful consolidation between the implicit and explicit SRTT conditions, and also call into question the existence of the phenomenon of wakeful consolidation on the SRTT entirely.

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Poster number: P-T015
Theme: Sensory & motor systems

Glia developmental plasticity couples learning and motor behaviour to reproductive needs

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During sexual maturation, the nervous system undergoes sexually dimorphic changes that couple behaviour to reproduction. Sex differences in behaviour include courtship, mating and cognitive-like processes such as learning that also enhance reproductive success. What are the precise mechanisms that generate sex-specific remodeling of behaviour and how universal are they?

Recently, we have identified a previously unknown sexual dimorphism in the C. elegans brain that is required for sexual conditioning, a form of associative learning by which a rewarding experience with mates overrides the effects of an aversive association with starvation. This behavioural flexibility allows males to prioritise mate over food location. We followed single cell development, from gene to circuit to behaviour, to define the neural basis of sex differences in learning. We found that sexual conditioning requires a pair of male-specific interneurons (termed MCMs) that are born during sexual maturation from differentiated, functional glial cells [1]. These glial cells are present in both sexes but re-enter the cell cycle to produce neurons only in males and this is regulated cell-autonomously by genetic sex. The MCM neurons remodel the integrative properties of pre-existing circuits present in both sexes to provide context-dependent behavioural plasticity.

Now we have found another pair of previously unknown male-specific neurons that also arise from glial cells, this time directly without a division. During sexual maturation, a class of differentiated, functional glial cells, undergo dramatic morphological and molecular changes becoming cholinergic sensory neurons that are incorporated into a sensory-motor mating circuit in the male. Functional imaging of neuronal activity combined with ablations and behavioural analysis suggest that these glia-derived neurons may act as proprioceptors to maintain sealed contact with the mate vulva during sperm transfer.

Our findings reveal an important role for glia developmental plasticity in the remodeling of circuits during sexual maturation that are essential for reproductive success.

[1] Sammut M, et al. Nature 2015;526:385–90.

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Poster number: P-T016
Theme: Sensory & motor systems

Phosphorylated histone 3 at serine 10 identifies activated spinal neurons and contributes to the development of tissue injury-associated pain

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Peripheral pathologies such as inflammation, nerve injury or cancer are associated with persistent pain. Effective control of persistent pain is an unmet medical need. However, the lack of satisfactory control of persistent pain has a detrimental effect on

quality of life and it generates undue demand on health and social services and ultimately from the society. Thus, the development of new analgesics is of paramount importance.

The development of persistent pain depends on post-translational and transcriptional changes in neurons involved in nociceptive processing. Transcriptional changes are particularly important for the maintenance of persistent pain. Superficial spinal dorsal horn neurons (SSDHN) form neuronal circuits that are essential to present nociceptive information to supraspinal centres hence for the development of the pain experience.

Epigenetic mechanisms including post-translational modifications in histones are pivotal in regulating gene transcription. Here, we studied whether phosphorylation of serine 10 (S10) in histone 3 (H3) that is involved in transcriptional changes in hippocampal neurons occurs in a group of rat SSDHN in peripheral pathologies.
We induced burn injury in or induced tissue inflammation without injury by injecting capsaicin into one of the hind paws. Both of burn injury and capsaicin injection induced prolonged up-regulation of p-S10H3 expression in a group of SSDHN. In contrast, brief thermal or mechanical nociceptive stimuli, which fail to induce tissue injury or inflammation, did not produce the same effect. Blocking N-methyl-D-aspartate receptors or activation of extracellular signal-regulated kinases 1 and 2, or blocking or deleting the mitogen- and stress-activated kinases 1 and 2 (MSK1/2), which phosphorylate S10H3, inhibit up-regulation in p-S10H3 as well as fos transcription, a down-stream effect of p-S10H3. Deleting MSK1/2 also inhibited the development of carrageenan-induced inflammatory heat hyperalgesia in mice. We conclude that p-S10H3 is a novel marker for nociceptive processing in SSDHN and play a crucial role in the development of inflammatory heat hyperalgesia.

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Poster number: P-T017
Theme: Sensory & motor systems

Dominance of non-dominant hemisphere in resting interhemispheric inhibition

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Transcranial magnetic stimulation (TMS) applied to one primary motor cortex (M1) exerts inhibitory effects on the contralateral hemisphere via transcallosal connections, giving rise to so-called inter-hemispheric inhibition (IHI). Previous studies have indicated that IHI effects are lateralised such that the dominant M1 (contralateral to dominant hand) exerts greater inhibition on the non-dominant M1. However, some contradictory results have been reported which may reflect differences in the TMS parameters that have been applied. Therefore, we investigated the role of the conditioning–stimulus (CS) intensity on the magnitude of the resting IHI elicited on dominant to non-dominant M1 and vice versa.

The level of IHI was measured in 17 right-handed participants by comparing motor-evoked potentials (MEPs) elicited by monophasic TMS when (i) a test stimulus (TS) was delivered over an individual M1, or (ii) the same TS was preceded (10ms) by a CS delivered to contralateral M1. CS and TS intensities were set to elicit MEPs of ~1mV in bilateral first dorsal interosseous muscles. In each subject, we recorded 30 trials of TS, and 30 trials of CS-TS, which were repeated for both hemispheres.

Repeated measure ANOVA showed MEPs decreased significantly when a CS preceded the TS, regardless of the hemisphere tested, confirming marked resting IHI ($p<0.001$). While the MEP reduction was greater when the CS was applied to the non-dominant hemisphere (TS to the dominant hemisphere), hemispheric effects remained statistically comparable ($p=0.084$). However, MEPs elicited by the CS varied across individuals and when CS difference across hemispheres was entered into the analysis as a covariate, a reliable interaction emerged ($p=0.031$). While MEPs were comparable following a single TS ($p=0.6$), MEPs were significantly smaller when the non-dominant hemisphere received the CS compared with the reverse situation ($p=0.013$).

These data suggest that, at rest, the dominant hemisphere shows susceptibility for receiving greater IHI than the non-dominant hemisphere when accounting for fluctuations in the intensity of the CS. We speculate that this relationship may reflect the greater flexibility of control over the dominant limb.

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Poster number: P-T018
Theme: Sensory & motor systems

Boosting upper-limb recovery after stroke by individualised selection of training conditions

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Upper limb hemiparesis is a common outcome of stroke, leaving many of the patients chronically impaired in performing basic daily life activities. In many cases the degree of hampered performance varies depending on movement parameters (e.g. target location and intended reach direction). Motor recovery can be improved by intensive practice and may further benefit from robot-assisted training. However, the degree of improvement may depend on the selection of practised movements. We hypothesized that motor learning and recovery would benefit from individually tailored training, by first mapping performance across a movement parameter workspace, and then practising movements that are located between sub-regions of better and worse performance.

We tested our hypothesis by comparing motor recovery of the upper limb in two groups of moderate-to severe chronic hemiparetic stroke patients (mean Fugl-Meyer upper-limb score: 21±12). Both groups received robot-assisted training, with 3 sessions per week for 5 weeks, and with weekly re-mapping of their performance across the whole workspace. Each movement was between a start location and a target 5cm distant, with levels of robotic assistance tuned to the patients needs, but held fixed throughout the protocol.

The test group (N=7) was trained with movements selected based on their performance maps, with the selection updated each week. The control group (N=9) received training with a standard protocol of “centre-out” reaching movements, from a fixed central location to radial target locations. Both groups improved average performance at the task, although individuals showed variable amounts of improvement in sub-regions of the map.

Following training, both groups also showed improvement in clinical scores of upper limb motor assessment, with an overall increase in Fugl-Meyer upper-limb sub-score of 3.1 (15%). However, training with performance-based selection of movements showed significantly superior recovery (23% compared to 10%, p=0.005, independent samples t-test), supporting our prediction.

In summary, rehabilitation based on performance-based criteria appears to be beneficial, and our novel method of mapping performance across the workspace may potentially serve as a diagnostic utility.

Supported by MRC.

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Poster number: P-T019
Theme: Sensory & motor systems

A previously unidentified parietal neuron promotes feeding in Lymnaea stagnalis

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Feeding in the pond snail (Lymnaea stagnalis) is controlled by a complex and distributed network of neuron types. This includes modulatory neurons that act on multiple functional groups, and can either promote or prevent feeding. The most thoroughly studied of these is the cerebral giant cell (CGC), which plays a permissive role in feeding, increasing excitatory output to the system when the animal senses food. Another modulatory cell, the pleural-buccal interneuron (PlB), has the opposite effect, by increasing inhibitory output when the animal receives an aversive touch, thus preventing feeding. A previously unidentified neuron, termed parietal dorsal 4 (PD4), has now been discovered, which can alter the tonic activity of CGC and PlB, thus giving strong influence over the entire feeding system.

Dye fills of PD4 reveal a bilaterally symmetrical cell with a soma on the dorsal surface of the parietal ganglion and an axon projecting through the pleural ganglion in to the cerebral ganglion. Electrophysiological recordings of PD4 in the isolated brain show a relatively negative resting potential with few spontaneous action potentials. When artificially depolarised, PD4 is capable of firing at high frequency (over 10Hz). Action potentials in PD4 result in short latency 1:1 EPSPs on the ipsilateral cerebral giant cell (CGC), suggesting a monosynaptic excitatory synapse. This causes a large increase in the firing rate of the CGC. In addition, a longer latency

inhibition occurs on the ipsilateral pleural-buccal interneuron (PlB), sharply reducing the neuron's tonic activity. Together both synaptic effects make feeding activity more likely.

Due to the powerful upstream effects of PD4 on the feeding system when active, and quiescence otherwise, it was hypothesised that this cell may be activated by chemical or tactile stimuli applied to the lips. When sucrose was perfused across the lips PD4 did not become active, despite an increase in the firing frequency of the CGC. A touch to the lips did reliably cause a small hyperpolarising input on PD4 with the cell remaining inactive. Further experiments will be needed to examine the functional role of PD4.

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Poster number: P-T020
Theme: Sensory & motor systems

Olfaction and hunger: an fMRI study on brain activity to appetising stimuli

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Food cues (particularly olfactory stimuli) are known to elicit hunger, indicating a strong link between the olfactory system and appetite, yet it is unclear at which level of olfactory processing this occurs. The olfactory pathway runs from the olfactory bulb to the piriform cortex and then to the orbitofrontal cortex. It is also closely connected to the nucleus accumbens, the amygdala, the hypothalamus, the anterior insula, and the hippocampus.

We conducted an fMRI study using food and non-food (flower) cues, presented in both visual and olfactory modalities. Data was acquired using a 3T Siemens scanner, a 32-channel head-coil, and a multiband EPI sequence with 1.5mm slice thickness designed to minimise susceptibility artefacts and provide good signal-to-noise in ventral olfactory-related brain regions. Twelve healthy subjects were presented with visual, olfactory or crossmodal (congruent olfactory and visual) stimuli of food or flowers in an event-related design with 5s stimuli and randomised inter-trial intervals. An MRI compatible olfactometer (ETT model 1) was used to present the olfactory stimuli. Participants also completed a hunger questionnaire, and provided pleasantness and intensity ratings of the olfactory stimuli. Analysis followed standard procedures for fMRI and included head motion correction, temporal filtering, registration to a standard template, and model-fitting with a general linear model. Group-level statistics used FSL's FLAME-1 model, and a (cluster-corrected) threshold of $Z < 2.3$, $p < 0.05$.

Voxelwise analyses of the data using participant hunger as a regressor revealed a significant increase in brain activity for food vs. non-food olfactory cues in the ventromedial prefrontal cortex. ROI analyses using the anatomically-defined olfactory-pathway regions mentioned above generally showed approximately equal responses to food and non-food stimuli.

Hunger affected brain activity to the appetising food smell stimuli in the ventromedial prefrontal cortex, but processing in the olfactory system appears unrelated to the edible or inedible aspect of the stimuli. This suggests that olfaction and appetite interact in multimodal brain regions (e.g. prefrontal cortex) and this activity is somewhat independent of lower-level sensory systems.

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Poster number: P-T021
Theme: Sensory & motor systems

Food leaving in C. elegans: a model of social interaction

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Nematodes respond to a range of environmental cues to elicit behaviours. This includes signals pertaining to the abundance and quality of their food source. The interaction of the free-living nematode Caenorhabditis elegans with its bacterial food source has been studied with a view to understanding the neural mechanisms that regulate its foraging behaviour. It has previously been shown that C. elegans will increasingly leave a bacterial lawn as the abundance of the bacteria becomes depleted (Milward et al., 2011, PNAS). Here we report a phenomenon that underpins a drive to leave food, which would allow for foraging in the animals

natural environment. We observed food-leaving behaviour of 7 adult worms placed on a defined bacterial lawn over a period of 24 hours. Surprisingly we found that the food-leaving rate increased over the 24 hour period even though there was no evidence for a depletion of the bacterial lawn. During this 24 hour period the adult worms had laid eggs which hatched into larvae therefore we tested whether or not the food-leaving response in the adult worms might be linked to the presence of larvae on the bacterial lawn. In support of this hypothesis we found that loading the bacterial lawn with larvae drove a food-leaving response in the adults. Furthermore, sterile adults did not exhibit this same enhancement in food-leaving after 24 hours. This suggests that food-leaving behaviour in adult C. elegans is triggered by their progeny. We have initiated an analysis of C. elegans mutants that show altered progeny enhanced food-leaving with a view to understanding the molecular mechanisms and inter-organismal signals that regulate this apparent social interaction. We have observed a role for neuropeptides in controlling this enhancement in food-leaving behaviour, with specific roles for orthologues of peptides involved in controlling human social interactions. We are also investigating the hypothesis that the C. elegans progeny involved in driving this enhancement in food-leaving produce an ascaroside signal, similar to dispersal signals that have previously been identified. This quantitative assay on interorganismal signalling will be used to better define the molecular, circuit and behavioural determinants of a simple model of social biology.
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Poster number: P-T022
Theme: Sensory & motor systems

Modulation food-dependent sensory integration in C. elegans

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Sensory inputs are integrated extensively before decision making converging in a multisensory processing and a final integration. Dysfunctional sensory signalling is associated with a number of disorders including autism spectrum disorders, schizophrenia, and anxiety. The molecular and cellular mechanisms underlying decision-making behaviours are beginning to be elucidated. In the nematode C. elegans decision-making is mediated by interneurons, integrating an array of synergistic and antagonistic inputs from sensory neurons. Food is a potent modulator of nematodes behaviour, and context dependent feeding and locomotion are underpinned by a number of well understood microcircuits. We have investigated these behaviours in mutants deficient in nlg-1 gene, the homologue of the human neuroligin implicated in autism. We identify that deficiency of this gene directly impacts on food dependent behaviours. This adds to the understanding of the pharyngeal and extra pharyngeal circuits that integrate the decision to feed. The nature and cellular basis of this food dependent behaviour reinforces a top down route that imposes regulation of pharyngeal dependent regulation of feeding. These data highlight specific details of how neuroligin organized sub-circuits in C. elegans. Further it provides better resolution of the behavioural expression of the molecular determinants that neuroligin support in C. elegans and higher organisms. Further the ability to manipulate rescue of nlg-1 deficiencies with human homologues provides a platform to investigate autism related mechanisms.

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Poster number: P-T023
Theme: Sensory & motor systems

The cellular mechanisms of a decision between incompatible behaviours in Lymnaea

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The decision to perform one behaviour often comes at the expense of performing another incompatible behaviour. A proposed mechanisms by which such decisions are made is via reciprocal inhibition between the networks involved in each behaviour. We looked at such behavioural choices in the model system Lymnaea stagnalis. This system provides an excellent opportunity to study such decision making processes due to the extensive knowledge of the neural control of many of its behaviour at the level of motoneurons, interneurons and modulatory neurons.

We looked at the two incompatible behaviours which serve opposite functions, ingestion and egestion. Ingestion has been extensively studied in Lymnaea, however the neural mechanisms of egestion have not previously been characterised.

We first looked at differences in the two behaviours in vivo and in semi-intact preparations. Feeding movements in Lymnaea consist of protraction and retraction of the radula from the mouth. Ingestion was characterised by contraction of the supralateral-radula tensor muscle (SLRT) in the retraction phase whereas during egestion, SLRT contraction occurred mainly in the protraction phase.

We further characterised differences in movements using an in vitro preparation where we were able to co-record activity on the SLRT with activity in the retraction phase muscle – the anterior jugalis muscle (AJM). Ingestion and egestion were triggered via artificial activation of the command-like interneuron CV1a or by tactile stimulation of the oesophagus respectively.

A motoneuron (B11) which innervates the SLRT was identified which underwent a phase shift in its activity between the two behaviours. We showed that via differential recruitment of projection interneurons, B11 received varying levels of excitation and inhibition in the protraction and retraction phases, thus determining the phase in which it was active.

Finally, we found that interneurons of the ingestion network had inhibitory connections with those in the egestion network, whereas those in the egestion network recruited a phase switching, plateauing interneuron to prevent activity in the ingestion interneurons. Thus preventing conflicting inputs to B11 during each respective behaviour.

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Poster number: P-T024
Theme: Sensory & motor systems

Magnetoencephalographic Study on Warmth Perception

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Warmth sensation is one of the basic sensory responses to maintain our body temperature and warn an injury from heating, however, the warmth perception has rarely been studied. Brain regions related to process the warmth perception are still controversial depending on warmth stimulators and neuroimaging methods. In this study, we developed a warm stimulator using a semiconductor diode laser. The cortical responses were recorded and analyzed by using magnetoencephalography (MEG).

The laser warm stimuli with 400 ms duration were irradiated on the index finger of thirty subjects. The subjects conducted three blocks of 50 trials. In each trial, the laser stimuli were delivered 50 times with 10 seconds inter-stimulus intervals. The subjects were asked to answer by pressing ‘yes’ or ‘no’ button.

The MEG signals segmented into epochs of 3 seconds before and 5 seconds after warm stimulation and a digital band-pass filter (0.02~40 Hz) was applied. Removal of eye and heart artifacts were processed by an independent component analysis method. Only the trials that subjects answered that they could feel warmth were selected for analysis. The cortical activations were investigated by analyzing event-related fields (ERFs) and time-frequency analysis.

In the ERFs, two components were found and their maximum peak appeared about 0.3 s and 1.3 s after the onset of stimuli. The cortical activation for the late component of ERFs were shown in the bi-lateral primary and secondary somatosensory cortex and ipsilateral primary motor and premotor cortex. In the time-frequency analysis, the amplitude of alpha and beta band started to decrease around 0.5 s after the onset of stimuli and its maximum suppression appeared at 1.1 s in the contralateral somatosensory sensors. In the cortical distribution of alpha oscillations, alpha event-related desynchonization (ERD) was found in the bilateral primary somatosensory cortex and inferior parietal lobule. The latencies of warmth-related ERFs and alpha ERD supports that the warm-specific unmyelinated C-fiber has slow conduction velocity. These MEG results provided additional information more than the previous EEG based reports.

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Poster number: P-T025
Theme: Sensory & motor systems

The novel cyclo-octadepsipeptide anthelmintic emodepside; mode and spectrum of activity

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Emodepside was launched as an anthelmintic for veterinary medicine in 2007. In 2008 we published the mode of action of emodepside showing that its ability to break resistance to all of the previously used anthelmintics was due to it exerting its action via an entirely novel mechanism 1,2: It is an activator of a class of voltage and calcium-gated potassium channels, SLO-1, that have a key role in regulating neuromuscular excitability 3. Thus activation of SLO-1 imparts neuromuscular paralysis on the nematode explaining the potent anthelminitic effect observed in vivo. The mode of action through SLO-1 was resolved using a forward genetic screen in the free-living nematode Caenorhabditis elegans and confirmed through heterologous expression of SLO-1 channels cloned from parasitic nematodes 4. Further studies investigating the selective toxicity of emodepside indicate it has a differential effect on nematode compared to human SLO-1 or Drosophila slo 5,6. To investigate whether this extends to other pest species of nematode we assayed the sensitivity of the plant parasitic nematode Globodera pallida to emodepside. The effects of emodepside on C. elegans feeding, reproduction, motility and viability was compared to its effects on G. pallida stylet thrusting, egg hatching, motility and viability. Emodepside had biological activity in all of the assays conducted for G. pallida and inhibited G. pallida motility and stylet thrusting with EC50 in the micromolar range and this was blocked by the SLO-1 antagonist verruculogen providing evidence for an action on SLO-1 in these effects. A bioinformatic search has identified an orthologue of C. elegans slo-1 in the G. pallida genome sequence. These data suggest emodepside impacts on G. pallida behaviours through a SLO-1 dependent mechanism.
Acknowledgement: Anna Crisford was supported on a Bayer funded graduate studentship. Caroline Rivers is supported by a Bayer BBSRC CASE studentship.

1. Guest, M. et al. Int J Parasitol 37, 1577-1588 (2007).
2. Harder, A., Bull, K., Guest, M., Holden-Dye, L. & Walker, R. in Antiparasitic and Antibacterial Drug Discovery: From Molecular Targets to Drug Candidates (ed Paul M. Selzer) 339-356 (Wiley-Blackwell, 2009).
3. Holden-Dye, L. et al. Inv Neurosci 7, 199-208 (2007).
4. Welz, C. et al. PLoS Pathog 7, e1001330 (2011).
5. Crisford, A. et al. Mol Pharmacol 79, 1031-1043 (2011).
6. Crisford, A. et al. PLoS Negl Trop Dis 9, e0004062, doi:10.1371/journal.pntd.0004062 (2015).

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Poster number: P-T026
Theme: Sensory & motor systems

Vision, decision, and navigation in mouse parietal cortex

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Many tasks in daily life involve a combination of perceptual decisions and navigation. Rodent parietal cortex has been implicated in both of these processes, with some studies focusing on its role in decisions and others on its role in navigation. Here we show that, when mice use vision to decide where to navigate, parietal cortex robustly encodes navigational, rather than perceptual or decision-related information. We trained mice in a two-alternative forced choice task, which required them to navigate in a virtual T-shaped corridor in which the correct choice was signaled by visual contrast on the corridor walls. 2-photon calcium imaging revealed that neurons in parietal cortex coded for combinations of the animal's position and heading direction in the virtual room, and their responses were highly predictable based on these measures. Different neurons exhibited diverse heading-position tuning, so the population as a whole could be readily decoded to predict the mouse's navigation paths in single trials. The neurons were also informative about the mouse's choice, but the choice could be easily predicted from heading-position trajectories of the mouse through the room. Spatial coding in parietal cortex required active navigation, not just vision: during playback of previous navigation scenes to passive mice, activity in visual cortex matched that during active behavior, but activity in parietal cortex did not. We conclude that when mice use visual information to guide navigation, parietal cortex encodes spatial factors rather than visual information or abstract decisions.

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Poster number: P-T027
Theme: Sensory & motor systems

XE 991, a KV7 channel blocker, acts as an otoprotectant in vitro

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Background
The aminoglycosides (AGs) are broad-spectrum antibiotics used for treating life-threatening Gram-negative bacterial infections. Whilst the AGs are highly efficacious, they have ototoxic side effects in a significant proportion of patients. The AGs enter sensory hair cells of the inner ear through their mechano-electrical transducer (MET) channels. Once inside the cell, they are thought to trigger mitochondrial dysfunction, thereby initiating apoptosis. To identify potential otoprotectants that might block AG entry by interacting with the MET channel we conducted a screen of the Tocris Ion Channel library.

Methods
Two assays were used, whereby gentamicin (a commonly-prescribed AG) was applied with or without the compounds for the duration of the experiment: 1) a 6-hour assay monitoring the death of zebrafish lateral line hair cells and 2) a 48-hour assay to assess the death of hair cells in mouse cochlear cultures. Electrophysiological recordings were carried out, examining ionic currents from mouse cochlear hair cells, to evaluate potential mechanisms of protection.
Results
Of the 160 compounds tested, 13 consistently protected mouse cochlear hair cells from 5 µM gentamicin when tested at a concentration of 50 µM. These 13 compounds were then re-screened at a higher concentration (100 µM) in the absence of gentamicin. Three of the 13 were without obvious toxic side effects and of these, all three protected at 10 µM, two at 500 nM, and only one (XE 991) at 10 nM. These three compounds were also protective at 100 µM against 10 µM gentamicin in the zebrafish assay.

Electrophysiological recordings revealed that only one of the compounds blocks the MET channels whereas all three block the basolateral potassium channels ($I_{K,neo}$) to varying degrees . For XE 991, which does not block the MET channel at 50 µM, the modest level of $I_{K,neo}$ block (~40% at 30 µM) argues against depolarisation as the mechanism of protection.

Conclusion
Our screen of known ion channel blockers has identified compounds that protect hair cells from AG-induced death in vitro. One of these, XE 991, protects hair cells at nanomolar concentrations and may prove to be a suitable lead compound for the development of a clinically viable otoprotectant.

Supported by the MRC.

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Poster number: P-T028
Theme: Sensory & motor systems

Physiological Characterisation of Subpallial Dopaminergic Neurons of Larval Zebrafish

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Dopamine (DA) is a highly conserved neurotransmitter that is involved in locomotion, emotion, learning and reward. Moreover, dysfunction of these neurons has been implicated in diseases including addiction, schizophrenia and Parkinson's disease. Our current understanding of DAergic neurons is largely derived from physiological and functional studies of mammalian midbrain DAergic neurons. However, these models have ethical and technical limitations: the study of mammalian DAergic neurons necessitates the use of invasive techniques that can cause suffering, harm and sacrifice of animals protected by the Animals (Scientific Procedures) Act 1986 (ASPA). Moreover, limitations associated with the accessibility of mammalian nervous tissue mean that it is currently not possible to conduct detailed in vivo analysis of DAergic neuron physiology. To address this issue, I am using early stage (larval) zebrafish that are not protected under ASPA as an ethically-oriented in vivo model for physiological analysis of DAergic systems.

Previous anatomical and genetic studies have suggested that a DAergic interneurons within the subpallium are equivalent to mammalian midbrain DAergic neurons. However, the physiology and behavioural function of these cells has not been investigated. Using Tg(ETvmat2:GFP) zebrafish, in which aminergic neurons express GFP, I have targeted subpallial DAergic neurons for in vivo electrophysiological study. I have characterised the endogenous firing patterns, membrane properties and connectivity of these cells. My findings demonstrate that DAergic neurons of the zebrafish subpallium are intrinsically excitable, exhibit endogenous firing and respond to behaviourally-relevant stimuli at an age when these animals are not protected under ASPA. These findings suggest that zebrafish can be used as an ethically-oriented model for detailed functional analysis of vertebrate DAergic systems.

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Poster number: P-T029
Theme: Sensory & motor systems

Upper Limb Motor Performance is not Predicted by Proprioceptive Acuity in Younger or Older Adults

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As we get older there is a decline in our ability to control simple and complex movements. Characterised by reduced speed and increased variability, these movement impairments can make it difficult to carry out activities of daily living and subsequently limit independence. Previous research has focused on a neuromuscular basis for these changes, and the contribution of somatosensory decline to this process is not well understood. Recently, it has been reported that proprioceptive acuity measured during passive wrist movement in the elderly is not predictive of their active motor performance. Here, we used a 2D robotic manipulandum device to investigate whether dynamic proprioceptive acuity could better predict reaching motor performance in older and younger adults.

Dynamic proprioception was measured using active movements of the unseen hand, guided through a constrained, smooth trajectory and ending at predetermined positions to either side of the visual target. Perceptual judgements regarding the hand's lateral position relative to the target were used to estimate systematic errors in perception of hand location (bias) and the region of low response reliability (uncertainty range). This was measured at 3 separate locations in the 2D workspace. Motor performance was assessed from the error in rapid reaching movements to targets at the same spatial locations, without constraint on the trajectory. Mean lateral deviation and variability of the end-point were correlated with proprioceptive acuity.

We found significant age related change in proprioceptive bias for physically inactive older adults only. However, using a multiple linear regression model, we found that neither proprioceptive bias nor uncertainty range were able to predict endpoint lateral deviation or variability, for either older or younger adults. We conclude that age-related proprioceptive decline assessed in passive or active conditions is not predictive of performance in fast, ballistic-type movements. However, its association with controlled movements that rely more heavily on sensory feedback should be investigated further.

Acknowledgments - This work is funded by the MRC-Arthritis Research UK Centre for Musculoskeletal Ageing Research (CMAR).

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Poster number: P-T030
Theme: Sensory & motor systems

Alterations to the somatosensory barrel cortex in mice at early adulthood following exposure to prenatal alcohol

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Children with fetal alcohol spectrum disorder (FASD) are known to have impaired sensory processing skills as a result of neurodevelopmental anomalies. The somatosensory barrel field in the neocortex of rodent is known to be susceptible to alcohol effects. Each barrel processes sensory input from 1 – 3 facial vibrissae, and within the barrel field, the posterior medial barrel subfield (PMBSF) contains barrels where tactile inputs from the large vibrissae on the contralateral side of the face of a rodent is processed. In studies on rat FASD models, prenatal and postnatal alcohol exposures significantly reduced the total area of the PMBSF, the area of individual PMBSF barrels, and the area of the septal portion of the PMBSF. The present study aims to provide further experimental data on the modification of the cortical barrels by investigating the effect of prenatal alcohol exposure (PAE) on C57BL/6J mice at early adulthood (PND 56) using a chronic alcohol paradigm. Pregnant mice, and their in utero litters, were

exposed to alcohol, through oral gavage (chronic alcohol, CA, group), on gestational days 7 – 16. Two control groups, an oral gavage sucrose control group (chronic alcohol control, CAc, group) and a non-treated control group (NTc group), were also examined. At PND 56, the left cerebral hemisphere of the pups from each group was stained for cytochrome c oxidase. The results showed reductions in the mean area of the PMBSF enclosure, total mean area of the PMBSF barrels, mean areas of the individual PMBSF barrels or mean area of the septal portion of the PMBSF in the CA group but was not significantly different from its controls. As the individual barrels are readily identified and have a specific nomenclature, specific individual barrels showed significant alterations in size with PAE. PMBSF barrels were smaller in the CA group compared to the CAc (74%) or the NTc group (56%). Although reductions in size were observed across barrel rows in the CA group compared to its controls, significant reductions in barrel sizes were observed in barrel rows D and E. This seems to indicate that PAE hinders PMBSF development which may explain the reason for the sensory-motor delays in children exposed to prenatal alcohol.

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Poster number: P-T031
Theme: Sensory & motor systems

Mirror neuron responses to facial expressions in autism spectrum disorder

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Mirror neuron system (MNS) is recognized as a network of premotor neurons that respond when one performs an action and observes that same action being performed by others. According to the simulation theory of the MNS, the observer 'simulates' the observed action in their own mind and predicts the actor's mental states (Gallese and Goldman, 1998). On this account, the MNS must play a key role in understanding the vast range of emotional information provided by the most important social stimulus, the human face. Understanding and reacting appropriately and immediately to the emotional expressions of interaction partners are key skills to build and sustain mutually satisfactory social interactions. Individuals with autism spectrum disorder (ASD), a condition characterized by difficulties in social interaction and communication, frequently exhibit atypicalities in the processing of social-emotional information. A dysfunctional MNS theory of emotion perception could account for some of the social difficulties associated with ASD. In fact, contradictory findings from past research investigating the MNS functioning in ASD reveal the need for further research to establish or rule out an impaired mirroring mechanism as a biomarker of ASD. In this study, EEG data were collected from 17 ASD and 16 neurotypical participants while they were presented with black-and-white photos of isolated eye and mouth images that had either a sad or a neutral expression. The observed MNS functioning signalled by mu suppression over the sensorimotor cortex in response to the face stimuli will be further investigated to identify any mu rhythm differences between groups (ASD vs. neurotypical), expressions (sad vs. neutral) and facial regions (eye vs. mouth). Understanding the neurophysiological mechanisms underlying the behavioural patterns which interfere with the diagnosed individuals' daily social functioning is vital to develop more effective intervention methods that directly address the causes of the ASD-related social difficulties.

References
Gallese, V., & Goldman, A. (1998). Mirror neurons and the simulation theory of mind-reading. Trends in cognitive sciences, 2(12), 493-501.

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Poster number: P-T032
Theme: Sensory & motor systems

C. elegans neuromuscular junction to investigate organophosphate intoxication

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Anti-cholinesterases including the carbamates and organophosphates (OPs) have an associated neurotoxic risk linked with their use as pesticides. In addition, OPs are also used in chemical warfare and terrorism. Current antidotes to such poisoning have limitations therefore new approaches are required. The inhibition associated to cholinesterases (ChE) leads to continuous stimulation of both nicotinic and muscarinic acetylcholine receptors due to the increase of acetylcholine in the synaptic cleft and resultant widespread life-threatening effects on neuromuscular, autonomic and central neurotransmission. We hypothesize that plasticity and associated

re-organization of the neuromuscular junction and other cholinergic synapses may provide distinct routes to understand and mitigate such toxicity. C. elegans is a model organism in which cholinesterase activity is pivotal to neuromuscular dependent behaviours and this can be readily observed in whole organism behavioural studies. This reinforces the wider value of this organism in studies of neurotoxication that readily translates to mammalian models1. Here we use quantitative assays of neuromuscular function in C. elegans to delineate the time-course and concentration dependence of the behavioural impact of ChE inhibition using the carbamate compound aldicarb. As previously observed1, we report that aldicarb impairs development and motility. In addition we quantify the inhibitory effect on pharyngeal pumping, a behaviour which underpins nematode feeding. The impact of the OP, DFP, is currently under investigation. Biochemical, transcriptional and genetic approaches will enable us to resolve organophosphate intoxicating pathways and adaptive mechanisms during prolonged exposure to ChE inhibitors.

1 Rajini, P. S., Melstrom, P. & Williams, P. L. A comparative study on the relationship between various toxicological endpoints in Caenorhabditis elegans exposed to organophosphorus insecticides. J Toxicol Environ Health A 71, 1043-1050, doi:10.1080/15287390801989002 (2008).

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Poster number: P-T033
Theme: Sensory & motor systems

Task-specific effects of cerebellar-transcranial direct current stimulation on motor control and learning

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The cerebellum plays an important role in motor learning and coordination, and is also implicated in many aspects of cognitive control. Electrical brain stimulation can modulate behaviour during certain motor and cognitive tasks. But the circumstances that lead to changes in behaviour need to be better understood if brain stimulation is going to hold promise as a therapeutic tool for patients with motor or cognitive deficits. The present study employed cerebellar-transcranial Direct Current Stimulation (c-tDCS) to investigate task-specificity during a motor adaptation task. Thirty-three right-handed participants in three separate groups (anodal, cathodal or sham) performed two different versions (easy and hard) of a centre-out joystick tracking task during two separate sessions (5-7 days apart, pseudorandomised across participants). Electrical stimulation (2 mA) was applied to the right cerebellar hemisphere online for 20 mins during session one only. Motoric effects (angular end-point errors between hand and eye) between the three groups during the two tasks, and over the two sessions were investigated. ANOVA revealed an effect of Session such that task accuracy was improved during session two more than during session one, attributable to learning. However, of special interest, an interaction between Group and Task ($F_{2,33} = 4.461$, $p = 0.042$), revealed that task accuracy was better after cathodal stimulation during the hard task, but not the easy task. This result strengthens the view that the inhibitory effects of cathodal c-tDCS during motor adaptation are specific to the level of task difficulty. This finding should be taken into account when designing training paradigms that involve the use of tDCS for therapeutic purposes in clinical populations.

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Poster number: P-T034
Theme: Sensory & motor systems

Analysis of spatial properties of perimeter units in the rostral thalamic nuclei

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The present study focused on exploring the properties of spatially related thalamic neurons (perimeter units) in terms of firing parameters and assessing their stability over time, after selected environmental changes (i.e. the presence or absence of the walls in the recording arena).

Experiments were performed on male Lister-Hooded rats, implanted unilaterally into the rostral thalamic area with tetrodes, mounted onto drivable 32-channel Axona (Axona Ltd., UK) microdrives. During the course of each recording session rats performed a pellet-chasing task and rostral thalamic single units were recorded (anteromedial and paratenial nucleus). During the recording trials we used 4 different arena types: full vertical perimeter (four walls present), no walls, partial perimeter (two walls present) and

full walled square with an object positioned on the arena's floor. After completion of the experiment the position of the recording electrodes was verified.

Single units were isolated using the cluster cutting tool in TINT (Axona Ltd., UK). A custom written MATLAB suite (NeuroChaT) was used for spatial analysis. As units were recorded over multiple days, the stability and verification of the same unit from one day to another were assessed using the Bhattacharyya distance between the clusters. A measure of cluster similarity was also assessed using the chi-square distribution of the Mahalanobis distance of the each spike points to the clusters. To analyse the effect of rotation of the partial wall on firing pattern of particular unit, we split the firing intensity map (heat map) into 16 sections. Each section was associated with the position of partial wall. Mean firing intensity in each section separately allowed us to trace/quantify changes in firing pattern which follows the rotation of partial walls in the recording arena.

We found that the rostral nuclei of thalamus contain spatially-responsive cells exhibiting the characteristic phenotype of the perimeter units. We were also able to quantify their firing properties (i.e. firing intensity and waveform stability) determined by the presence or absence of arena walls and their position.

Supported by The Welcome Trust and Science Foundation Ireland.

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Poster number: P-T035
Theme: Sensory & motor systems

Predisposition to anomalous experiences: An investigation using transcranial direct current stimulation

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Introduction/Rationale: "Anomalous" experiences (AEs) are common in several psychological and neurological disorders, but are also experienced with surprising frequency by many people in the absence of such disorders. The phenomenology and cognitive mechanisms of AEs do not appear to differ significantly between clinical and non-clinical groups. One mechanism by which AEs can arise is known as "cortical hyperexcitability" (CHE); heightened activation of cortical neurons. It is vital to explore how CHE influences conscious perception in non-clinical groups in order to compare data with clinical groups and produce findings relevant for the majority of the population.
Methods: A within-participants design was used. 62 participants (77% F, $\bar{x}$ age=20yrs) completed two questionnaire measures exploring predisposition to AEs; "Cardiff Anomalous Perceptions Scale" and "Cortical Hyperexcitability index". Participants underwent single-blind anodal (20 mins, 1.5mA) and sham (30s, 1.5mA) tDCS (anode at Pz, cathode at Cz), and completed the Pattern Glare (PG) task 20 mins after stimulation onset. PG task involves rating intensity of anomalous visual distortions (AVDs) experienced when viewing striped gratings (medium/ high frequency). Positive medium-high differences (M-HΔ) in intensity ratings indexes CHE.
Results: Mean CHi and CAPS scores were 51 (16%) and 49 (10%) respectively, and significantly correlated with one another ($r= 0.69$, $p<0.01$). AVD M-HΔ intensity rating correlated significantly with CHi "positive aberrations" factor scores under anodal stimulation only. A quartile split of overall CHi scores identified extreme high/low scores (Q1=0-25,n=15; Q4=75+,n=15) and these scores were used to split the sample. High CHi scorers rated AVD M-HΔ as more intense under anodal stimulation (and vice versa for low CHi scorers). AVD M-HΔ difference between quartiles only approached significance under anodal stimulation.
Conclusions: CHi and CAPS scores support the notion that psychologically-normal samples experience AEs. Interestingly, data trends suggest that Q1/Q4 may respond differently to tDCS. High latent CHE in Q4 may facilitate the effects of anodal stimulation (due to insufficient inhibition). This would support screening of tDCS participants for CHE in future research.

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Poster number: P-T036
Theme: Sensory & motor systems

The Effect of Emotion on Multisensory Integration and its Neural Correlates

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The ability to integrate multiple sensory signals into one unitary percept is crucial to have a coherent understanding of the world around us. Limited past research has investigated how cross-modal, emotion-laden sensory signals are integrated to influence

perceptual processes. Such work has so far demonstrated that facial and vocal expressions are combined and can interact during emotion perception. These studies have observed enhanced multisensory integration, measured by judgment accuracy and speed. However, even fewer studies have investigated the precise time-course of emotion integration. Therefore, the current study (N = 25) used EEG to examine event-related potentials (N170 and P100) during emotional face processing, when the faces are preceded by congruent and incongruent emotional sounds (happy/sad). Analyses will focus on comparing differences in the mean amplitude and latency of the N170 and the P100, across emotionally congruent and incongruent conditions. We expect that the emotion-laden sounds, like crying, would adapt the visual perception of emotional faces, such that happy faces would appear less happy after listening to a sad sound, and vice versa. We also expect that this integration would result in differences in the neural correlates of emotion processing. Our results will have direct implications for understanding how emotion processing can influence multisensory integration.

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Poster number: P-T037
Theme: Sensory & motor systems

Distribution of visual and locomotion signals in mouse superior colliculus

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The superior colliculus (SC) is both a sensory and motor structure. The superficial layers receive input from the retina and visual cortex, while the intermediate and deeper layers include neurons that are sensitive to multiple modalities, and are more strongly linked to motor output. However, we do not know how the relative influence of visual sensory signals and modulatory (such as those correlated with locomotion) signals depend on depth within SC. We made extracellular recordings from 404 single- and multi-unit clusters at up to 2.5mm below the surface of SC using chronically implanted tetrodes in 3 awake mice. Mice were head-fixed and allowed to run on a treadmill during presentation of visual stimuli (flashes of large white or black discs), or moved freely around a patterned square arena, in the light or in the dark. As expected, visual responsivity decreased with depth from the surface of SC, but robust visual responses could be observed at least 1 mm below the surface of SC. Visual latency was near 20 ms in superficial layers, and increased slightly in deeper layers. Pearson's correlation between neural activity and movement speed was positive, on average 0.06 (s.d. 0.12) in freely moving animals and 0.02 (s.d. 0.11) in head-fixed animals, and increased slightly with depth. Correlations between neural activity and movement speed in freely moving animals were similar in presence and absence of light. We conclude that visual responses are faster and stronger in the superficial layers of SC, and that locomotion related activity may be stronger in deeper layers.

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Poster number: P-T038
Theme: Sensory & motor systems

Interactions between rat primary motor (M1) and sensory (S1) cortex at delta, theta and gamma frequency in vitro

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Topographic maps of sensory and motor neocortical regions are well established, however, connections between M1 and S1 are relatively underexplored at the neuronal network level in in vitro. The current study investigates the role of connections between M1 and S1 during pharmacologically-induced persistent oscillatory network activity. Local field potentials (LFP) were recorded in deep layers (V) of M1 and S1 in sagittal brain slices (450 µm) obtained from male Wistar rats (50-75 g). Intact and cut/regionally isolated slice preparations were used in the study. Theta (6-12 Hz) and gamma (30-40 Hz) oscillations were induced by bath application of kainic acid (KA; 150 nM) and carbachol (CCh; 2-10 µM). Low dopaminergic and low cholinergic states were required to induce delta oscillations. In both M1 and S1, initial theta (M1 6.5 ± 0.2 Hz; S1 7.1 ± 0.5 Hz) and gamma (M1 33.7 ± 0.7 Hz; S1 34.7 ± 1.8 Hz, n=10) activity was induced by application of CCh (2 µM) and KA (150 nM) and subsequent application of dopamine antagonists SCH23390 (10 µM) and haloperidol (10 µM) slowed the activity to 5-10 Hz and 20-30 Hz prior to emergence of large amplitude delta (M1 3.1 7.3 ± 0.2 Hz; S1 3.2 ± 0.7 Hz) oscillations. Pharmacological studies suggested the involvement of GABA, AMPA and NMDA receptors in generation of theta and gamma oscillations in both areas, whilst delta activity did not require NMDA receptors. Correlation studies and cut/isolated slice preparation studies revealed that local neuronal networks in deep layers of M1 are the likely source of delta activity in both M1 and S1, unlike theta and gamma oscillations which originated from deep layers of S1 in the intact slice preparation. Cuts placed between both regions suggest both M1 and S1 have local independent network theta

and gamma generators. These data indicate that both M1 and S1 exhibit theta, gamma and delta oscillations in vitro, and that each region may lead or lag the other, depending on the oscillatory regime.

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Poster number: P-T039
Theme: Sensory & motor systems

Fluoxetine depresses response to visual stimuli in the superior colliculus: potential implication for pharmacotherapy of ADHD

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Attention deficit hyperactivity disorder (ADHD) is a persistent neurodevelopmental disorder which causes impairment across the lifespan. Current estimates show a prevalence rate of ADHD of 5-10% in children with psychostimulant medication used to treat up to two thirds of patients. Though the efficacy of psychostimulant medication (such as D-amphetamine) in relieving ADHD symptoms has been repeatedly demonstrated, the abuse potential of psychostimulants has emphasised the need to identify therapeutic interventions with safer profiles. A key step in this process is identifying drugs with similar neural targets. Recent evidence suggests that the midbrain superior colliculus a sensory structure associated distractibility – may be one such target. Electrophysiological observations in the rat have shown that D-amphetamine depresses visual activity in the superior colliculus (SC). This depression is reversed following the introduction of the broad spectrum 5-HT antagonist metergoline, suggesting that D-amphetamine's action at the level of the SC is 5-HT mediated. To further explore the possibility of drugs acting on 5-HT-mediated transmission as therapeutic agents in ADHD, the present study investigated the effect of the 5-HT uptake inhibitor fluoxetine on SC visual responses in the anaesthetised rat. Fluoxetine was administered alone at a range of doses (i.v.), and was compared to vehicle and fluoxetine administered in the presence of NAD-299 (a highly specific 5-HT1a antagonist), to block 5-HT autoreceptors. Whilst fluoxetine alone had little effect, NAD-299 followed by fluoxetine resulted in a dose dependent depression of visual activity with a profile closely resembling the D-amphetamine effect. The results suggest that a focus on 5-HT drugs may be a useful route to safer therapies for ADHD.

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Poster number: P-T040
Theme: Sensory & motor systems

Positive modulation of Kv3 K+ current prevents bursting and maintains regular action potential timing following exposure to loud sound

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Action potential timing is essential for accurate sound processing by the dorsal cochlear nucleus (DCN), an auditory brainstem structure involved in sound localization in the vertical plane. Previous studies have shown that exposure to loud sound leading to hearing loss and tinnitus increases neuron excitability and network synchrony in the DCN. We have previously shown that DCN fusiform neurons change from a regular to burst-like firing pattern in response to acoustic over-exposure, and this is associated with a down-regulation of Kv3-like K+ currents (Pilati et al., 2012). Here we test whether AUT1, a positive modulator of Kv3 K+ currents (Rosato-Siri et al., 2015) prevents fusiform cell bursting activity that can be observed following partial inhibition of K+ currents with tetra-ethyl-ammonium (0.5 mM TEA) or following acoustic over-exposure. Whole cell current clamp recordings were made from DCN fusiform cells of CBA mice (post-natal day 14 to 19), in vitro. Action potential regularity was measured within and across stimulus trains, using coefficient of variation and coincidence ratio methods, respectively. We show that partial block of K+ currents or exposure to loud sound similarly reduced the overall firing frequency, decreased the action potential afterhyperpolarisation and disrupted action potential regularity. AUT1 (30 µM) applied in the presence of TEA, or following acoustic over-exposure did not affect firing frequency. However, AUT1 rescued action potential afterhyperpolarisation and restored a regular action potential firing pattern, preventing the occurrence of bursts in both conditions. In conclusion, positive modulation of Kv3 K+ currents has the potential to rescue deficits in sound discrimination that occur following acoustic over-exposure.

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Poster number: P-T041
Theme: Sensory & motor systems

Modulation of pharyngeal excitability and feeding behaviour by Zinc pyrithione

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Zinc pyrithione (ZP) is an antimicrobial and antifungal compound which is the active constituent of anti-dandruff shampoo. ZP interacts with mammalian voltage-gated potassium channels (Xiong et al., 2007) and we have shown it is an activator of KQT-1, a C. elegans orthologue of mammalian KCNQ potassium channel. kqt-1 is expressed in mechanosensory neurones and pharyngeal muscle therefore we tested the effect of ZP on feeding behaviour. ZP impairs C. elegans feeding and this is partly phenocopied in a kqt-1 mutant which is defective in dynamic regulation of pharyngeal pumping. Moreover, actions of ZP are occluded in the kqt-1 mutant suggesting a role for KQT-1. Using NeuroChip (Hu et al., 2013) we show ZP treated animals have a lower frequency of EPGs (ElectroPharyngeoGram), indicating that ZP inhibits pharyngeal activity. Additionally we have found that ZP causes larval arrest and we are investigating whether or not this is related to its inhibitory effect on the pharyngeal system.

Overall, these data suggest that the antimicrobial compound ZP additionally has efficacy against the free-living nematode C. elegans by impacting on the pharyngeal microcircuit and impairing its ability to feed. This has implications for the discovery of new nematicidal targets and may also have relevance to the ecotoxicity of ZP, a widely used antimicrobial agent.

Acknowledgements: We gratefully acknowledge the C. elegans Genetics Centre (CGC) for kqt-1.

Hu C, Dillon J, Kearn J, Murray C, O'Connor V, Holden-Dye L, et al. (2013) NeuroChip: A microfluidic electrophysiological device for genetic and chemical biology screening of Caenorhabditis elegans adult and larvae. PLoS ONE 8 e64297.

Xiong Q, Sun H, Li M (2007) Zinc pyrithione-mediated activation of voltage-gated KCNQ potassium channels rescues epileptogenic mutants. Nat Chem Biol 3: 287-296.

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Poster number: P-T042
Theme: The neurobiology of stress

CACNA1C dysfunction: impact on adult neurogenesis?

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Large-scale genetic studies have identified variation in the gene calcium voltage-gated channel subunit alpha1C (CACNA1C) to substantially increase risk for psychiatric disorders. CACNA1C encodes an alpha-1 subunit of voltage-dependent calcium channels which mediate calcium influx into cells. This influx can be regulated by the HPA axis, suggesting that CACNA1C may be susceptible to environmental factors. Adult neurogenesis occurs in the dentate gyrus of the hippocampus. This neurogenesis is associated with normal cognition and hippocampal plasticity and may underlie impairments in cognitive behaviours in psychiatric disorders. The aim of this research is to assess how CACNA1C dysfunction may occur following an environmental insult and investigate any impact on neurogenesis.

Methods
Wild-type rats were subject to a series of stressors pre-puberty (PND26-28) and assessed for CACNA1C mRNA expression in adulthood. CACNA1C heterozygous knock out rats (CACNA1C +/-) were acquired from Sage Laboratories, USA and their dentate gyri examined for neurogenic markers.

Results
Prepubertal stress in wild-type rats resulted in decreased mRNA expression of CACNA1C in the Cornu Ammonis 1 ($F = 14.8$, $p = 0.0017$) and Cornu Ammonis 3 ($F = 4.9$, $p = 0.04$) subfields of the hippocampus. CACNA1C +/- rats show a 50% decrease in the neurogenic cell proliferation marker BrdU ($F = 5.265$, $p = 0.039$). However there was no difference seen in doublecortin ($F = 0.04$, $p = 0.84$). The impact of this defect on neurogenic dependent behaviours will also be presented.

Discussion
We demonstrate that prepubertal stress can result in significant decreases of CACNA1C hippocampal mRNA expression. Early life stress is associated with deficits in adult neurogenesis (Naninck et al., 2015). Dysfunction in the CACNA1C gene led to a decrease in cell proliferation in adult neurogenesis. However, there is no difference in the total number of immature neurons, suggesting that this decreased proliferation may be compensated by a lack of apoptosis. The mechanism surrounding this effect requires further analysis to determine if decreased CACNA1C following stress drives the neurogenesis deficit.

Reference
Naninck et al (2015) Hippocampus 25:309–328.

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Poster number: P-T043
Theme: The neurobiology of stress

Low-dose photon irradiation alters neurogenesis via modulating membrane conductance

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The development of the central nervous system strongly depends on carefully coordinated processes like proliferation, differentiation and migration (Götz & Huttner, 2005). It is a known issue that especially the process of neurogenesis is dependent on a variety of external and internal factors (T. Huang et al., 2012; Le Belle et al., 2011). In this context, a number of studies support the hypothesis that ionizing radiation (IR), persistently reduces the pool of neural stem cells (NSCs) in the subventricular zone and progenitor cells in the dentate gyrus of the hippocampus, which may explain mental deficits observed in patients treated with radiotherapy during neurogenesis (T.-T. Huang et al., 2012; Rodgers et al., 2013). Until today the precise mechanisms by which radiation results in a markedly increased level of mental disorders are poorly understood. Increasing evidence suggests that the activity of ion channels is intimately related to the control of proliferation and also the regulation of differentiation depends on the activity of ion channels (Giachino et al., 2014; Shimazu et al., 2005). In a previous study we showed that low-dose IR results in an immediate increase in the conductance of the human intermediate-conductance potassium channel hIK, which is a prominent regulator of cell motility and differentiation (Roth et al., 2014). The aim of the study is to understand if IR leads to similar effects in the biophysical properties during neurogenesis in embryonic and in adult NSCs. Therefore we characterized the profile of membrane currents during differentiation of a J1 derived neural stem cell line, using the whole-cell patch clamp technique. We indicated three different main conductances carried by K+-channels in J1-NSCs which show an increase during differentiation. The same increase in conductance can also be detected 24h after irradiation of these stem-cells at a dosage lower than 0.5 Gy or upon treatment with the nitric oxide (NO) donor NOC-18, especially by the voltage-gated potassium channel Kv3.1. Furthermore, the same treatment showed the occurrence of the neurogenesis marker doublecortin. These results lead to the assumption that clinical-relevant radiation doses induce differentiation via Kv3.1 channels mediated by NO signaling.

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Poster number: P-T044
Theme: The neurobiology of stress

Adrenal-dependent regulation of glutamaergic-related plasticity: impact of endogenous glucocorticoids on natural synaptic activity

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Glucocorticoids (GC) [expressed as CORTisol-man; CORTicosterone-rodent] are fundamental for the regulation of the body's stress response, and act through endogenous receptors to modulate physiological functions such as learning and memory via experience-dependent synaptic plasticity. This well-established mechanism for learning and memory processing is regulated by the actions of molecules like glutamate receptors, and effects of stress on neuronal plasticity, particularly synaptic potentiation processes is via modulation of glutamate receptor actions. Athough actions of stress-level GCs on neuronal plasticity have been reported; typically in vitro and ex vivo, the role of GCs in mediating these receptor-dependent actions, as well as its effects on key components of an activated synapse has not been fully deciphered in vivo. Here, we assessed the influence of physiological stress on the regulation of well-characterized modulators of synaptic potentiation (GluA1 and PKA activity) at the gene and protein level. We further examined

the effects of stress exposure on important synaptic plasticity processes i.e. GluA1 trafficking across the synapse, and stimulus-driven regulation of sub-unit specific receptor activity. Radioimmunoassay analysis of plasma cort revealed a significant induction (46.8±29.01 rising to 1358±260.8 ng/ml; $p < 0.001$) in cort levels post stress exposure. Data on expression dynamics of the investigated synaptic plasticity-associated molecules revealed adrenal-glucocorticoid mediated up-regulation of the studied genes in the hippocampal transcriptome [gria-1 peak at 180 min ($p<0.001$) and pkaca peak at 360 min ($p<0.001$)]; closely followed by expression of the corresponding translated/ activated protein in the same region. Kinetics of the studied genes and proteins were adrenal hormone-mediated as no observable changes in transcript or protein expression were noted in hippocampus of adrenalectomised animals. Sub-cellular fractionation experiments confirmed that stress-level GC exposure triggers the synaptic exocytosis of calcium permeable AMPARs, a feature that relates to synaptic potentiation processes. Thus we provide in-vivo evidence for adrenal-glucocortioid dependent potentiation of natural synaptic activity during periods of high arousal.

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Poster number: P-T045
Theme: The neurobiology of stress

Different allostatic load markers predict grey and white matter integrity measures in the ageing Whitehall II cohort

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Introduction: Evidence of changes in brain anatomy and mental health following traumatic stress in patients with post-traumatic stress disorder, mood or personality disorders exists, but little is known about the association between everyday stress and brain structure in the general population. The secondary stress (allostatic load) markers, Allostatic Load (AL) index, Metabolic Syndrome (MetS) and Framingham Stroke Risk score FSRS) were selected as potential predictors of structural grey and white matter (GM, WM) integrity at follow-up, in Whitehall II (WHII) Imaging Sub-study participants (1,2).

Methods: T1 and DTI scans from 349 WHII participants (69.6 ± 5.2yrs, 305 males) were analysed (1-2). The sum of AL index, MetS and FSRS were calculated from two WHII phases, up to 10 years before the scan. The effect of each secondary stress marker was assessed using F-tests and linear associations between the markers and GM density (FSL-VBM) fractional anisotropy and mean diffusivity (FA, MD in FSL-TBSS) controlling for the other markers and socio-demographic variables (multiple comparison corrected, significance level TFCE $p<0.05$).

Results: AL index, the most closely linked measure to allostatic load, was the most important marker for predicting low GM integrity, and FSRS for predicting widespread, low WM integrity (Fig.1), most likely via risk, which is often associated with micro-vascular changes.

Conclusions: The three secondary stress markers are linked through the concept of allostatic load but with different measures of structural brain integrity, possibly by different physiological pathways.

References:
1. Filippini, N. et.al. 2014: BMC Psychiatry. 14:159-175.
2. Marmot, M. & Brunner, E. 2005: Int J Epidemiol. 34: 251-256.

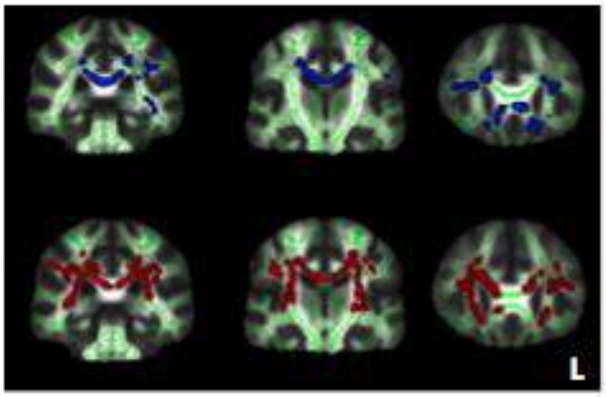

Fig 1. Significant association of FSRS with low FA (in blue) and high MD (in red) values after controlling for MetS, AL index, and socio-demographic factors. Multiple comparisons corrected, TFCE, $p < 0.5$. Significant regions are dilated for illustrative purposes, overlaid on a green skeleton.

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Poster number: P-T046
Theme: The neurobiology of stress

Molecular Changes in the Adult Brain Resulting From Inappropriate Fetal Glucocorticoid Exposure

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Prenatal stress or inappropriate fetal glucocorticoid (GC) exposure increases susceptibility to neuropsychiatric disorders in later life. The developing brain is normally protected from GC by the enzyme 11β-Hydroxysteroid Dehydrogenase 2 (HSD2) which inactivates GC to inactive 11-dehydro forms. HSD2 is expressed throughout the fetus in early to mid-gestation, after which its expression declines. Removal of HSD2 specifically from the mouse brain (HSD2BKO) results in depressive-like behaviour and a mild memory deficit in adults1.
To investigate the molecular mechanisms underpinning the HSD2BKO phenotype, RNA-seq analysis was carried out on the hippocampi (a brain region important in mood and cognition) of HSD2BKO and littermate control mice. This analysis found 2359 genes differentially expressed (raw p<0.05) but only 37 remained after repeated sampling adjustment (adj P<0.05).
6 genes were taken forward for RT-qPCR validation of the RNA-seq result. Of these, only the result for Akt2 has been verified as it was found to be up-regulated in the hippocampus of HSD2BKO mice (P=0.022). Akt2 is a protein kinase involved in cell survival and metabolism. Akt2 deficient mice display anxiety and depressive-like behaviours as well as insulin resistance. Components of the PI3K/Akt pathway were analysed by RT-qPCR and GSK3β was found to be down-regulated in the cerebellum of HSD2BKO mice (P=0.0004). GSK3β is regulated by Akt and has been implicated in neuropsychiatric disorders. In a rodent model of juvenile stress, GSK3β was found to be down regulated in the hippocampus.
These data suggest a possible role for Akt2 signalling in mediating the neurological effects of inappropriate prenatal GC exposure.
Work supported by WT project grant (MCH), BSN project support grant (MCH) and a Centre for Cognitive Ageing and Cognitive Epidemiology MRC PhD studentship (FS).
1. Wyrwoll, C. et al. Fetal brain 11β-hydroxysteroid dehydrogenase type 2 selectively determines programming of adult depressive-like behaviors and cognitive function, but not anxiety behaviors in male mice. Psychoneuroendocrinology 59, 59–70 (2015).

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Poster number: P-T047
Theme: The neurobiology of stress

Gender-associated neurophysiological differences in neurons of the bed nucleus of the stria terminalis (BNST): a brain slice study

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The BNST is a nucleus in the limbic forebrain that plays a role in stress, fear and anxiety. The BNST is also sexually dimorphic and has been implicated in determination of sexual identity. As well as acting a major output pathway for the amydala, this nucleus is thought to act as a relay for cortical and limbic control of hypothalamic function, in particular the HPA axis. Even though the sexually dimorphic properties of this region are well known, to our knowledge, the cellular electrophysiological properties of BNST neurons has not been examined previously in females. Amongst the human population, females are far more susceptible to developing anxiety related disorders. Given the fact that the BNST plays a key role in anxiety and is also sexually dimorphic examining the differences in the electrophysiological profile could be of great benefit in examining this altered susceptibility.

This study examined the effect of gender on the intrinsic properties of BNST neurons. In vitro patch clamp recordings were made from 300□m coronal brain slices prepared from either adult male or female mice aged 3-5 months. At a set pre-stimulus membrane potential of -80 mV the action potential waveform properties were examined and a more depolarised threshold was observed in the female cohort (male -54 ± 1, female -52 ± 0.5)

To examine excitability, incremental depolarizing current stimuli (5-80 pA) lasting 500 ms were applied to BNST neurons at -80 mV. As the amplitude of the stimulus was increased, both the probability and the rate of AP production rose. A higher proportion of cells from the male animals fired in response to a number of the depolarising steps. This was most evident with the +20 pA step (male 18/40 cells, female 34/150 cells). It is quite likely the key underpinning factor in this gender-dependence difference in the spike output was the more depolarised threshold in the females BNST neurons. Consequently, it would be interesting to understand the cellular basis of this difference. Certainly these gender-associated differences in cellular neurophysiology are likely to contribute to sex –associated differences in limbic influences on HPA axis function.

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Poster number: P-T048
Theme: The neurobiology of stress

Stress effects on Brain Connectivity

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Background: Stress is essential for survival as it enables increased alertness, focussed attention and heightened cognitive processing, in the presence of a threat from the external environment. The stress response is mediated by the HPA axis, which releases the glucocorticoid (GCC) stress hormone, cortisol (CORT; corticosterone in rats) into the circulation. The HPA axis is under both circadian (24 hour) and ultradian (~hourly) control, and this pattern of GCC release is important for good health. Patients who suffer from conditions where healthy HPA axis function is altered, such as Addison's disease, experience extreme fatigue, severe weight loss and lack of motivation amongst other symptoms. GCCs have long been showed to act on the brain and their action is mediated by specific receptors, the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR). These receptors have varying distribution across the brain and different affinities for GCCs, properties to which we can attribute the fact that different brain regions respond to GCCs in different ways.
Aims: Here we aimed to use resting state functional magnetic resonance imaging (fMRI) to show that the pattern of GCC circulation affects large scale resting state networks.
Methods: We conducted a randomised, double-blinded, placebo-controlled, three-way crossover investigation with 15 healthy, male, right-handed volunteers. Each volunteer underwent three administration schemes of hydrocortisone replacement (total daily dose 20mg). These were organised into three arms: (1) oral administration, in line with current therapeutic protocol for patients who receive GCC replacement (2) continuous administration via a subcutaneous pump and (3) pulsatile administration via a subcutaneous pump. All participants underwent a resting state functional magnetic resonance imaging (fMRI) scan on the final day of each arm. The data presented here is a FEAT (FMRI Expert Analysis Tool) analysis (FSL software) at individual and group levels with a focus on the dorsal striatum, hippocampus and anterior cingulate cortex as regions of interest.

Results: The results of our study suggest that the pattern of GCCs influences the resting state activity in regions of the brain that are known to be glucocorticoid sensitive and involved in emotional processing and motivation.
Conclusions: thereby highlighting how stress hormone pulsatility plays a significant role in cognition.

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Poster number: P-T049
Theme: The neurobiology of stress

Exposure to repeated restraint stress modulates the hippocampal nitrergic system and upregulates protective antioxidant genes in the rat

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Increases in hippocampal neuronal nitric oxide synthase (NOS) derived-nitric oxide (NO), a free radical with both physiological and pathological functions, has recently been shown to mediate chronic stress-induced depressive-like behaviour in rodents. However, we have previously demonstrated that a single acute stress decreases neuronal NOS expression in the hippocampus despite increased concentrations of NO metabolites (NOx) and nitrosative status. To identify if reductions in neuronal NOS are isolated to a single stress exposure, this present study utilised a model of repeated restraint stress to demonstrate the temporal changes in oxidative/nitrosative stress and antioxidant gene expression occurring in the hippocampus. Male Wistar rats were subject to control conditions or 6 hours of restraint stress applied for 1, 2, or 3 days (n=8 per group) after which the hippocampus was isolated for fluorescent and colorimetric assays of oxidative/nitrosative status, and relative gene expression. A single stress exposure produced highly significant increases in nitrosative status ($p<0.001$) and NOx ($p<0.01$), with subsequent episodes of restraint resulting in sustained increases in 3-nitrotyrosine ($p<0.01$), indicative of higher concentrations of NO. Despite these increases, expression of neuronal NOS decreased over all stress treatments ($p<0.05$). However, both inducible NOS ($p<0.05$), and the NOS-independent NO generator, xanthine dehydrogenase ($p<0.05$), increased significantly following stress exposure. In addition to the overall increase in nitrosative stress, exposure to restraint significantly decreased hippocampal concentrations of reduced glutathione ($p<0.05$) across all time points measured. This was accompanied by transient increases in expression of the major antioxidant regulatory pathway members, nuclear factor (erythroid-derived 2)-like 2 ($p<0.01$), NAD(P)H dehydrogenase [quinone] 1 ($p<0.01$), and haem oxygenase 1 ($p<0.01$). Together, these results demonstrate that decreases in hippocampal neuronal NOS are not restricted to a single stress exposure, with repeated restraint also causing increased NO production from inducible and alternative sources resulting in sustained protein nitrosylation, oxidative/nitrosative stress, and expression of antioxidant genes.

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Poster number: P-T050
Theme: The neurobiology of stress

Hypertension and cardiovascular changes evoked by chronic stress in female rats: comparison of homotypic vs heterotypic chronic stress regimes

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Aim: To evaluate the impact of two chronic stress regimens (homotypic and heterotypic) in cardiovascular function of Wistar (normotensive) and spontaneously hypertensive (SHR) rats.

Methods: Age-matched (60-days-old) female Wistar (n=21) and SHR (n=21) rats were divided into 3 groups (n=7 per group): (i) control, (ii) repeated restraint stress (RRS, homotypic stressor), and (iii) chronic variable stress (CVS, heterotypic stressor). The animals were subjected to daily sessions of stress for 10 consecutive days. The RRS animals were restrained daily for 60 minutes. The CVS consisted of twice daily exposures to alternating stressors. Cardiovascular recording was performed on the 11th, 24h after surgical cannulation of the femoral artery.

Results: SHR presented higher basal plasma corticosterone concentration than the normotensive rats ($P<0.05$). Moreover, RRS and CVS increased plasma corticosterone levels in both normotensive (RRS: $P<0.05$, CVS: $P<0.05$) and hypertensive (RRS: $P<0.01$, CVS: $P<0.05$) strains. As expected, SHR rats of all experimental groups showed higher arterial pressure than Wistar rats ($P<0.01$). However, neither RRS ($P>0.05$) nor CVS ($P>0.05$) significantly affected arterial pressure in either normotensive or SHR rats. However,

although absence of strain differences in heart rate baseline, RRS increased values in both normotensive (P<0.001) and SHR (P<0.05) rats. The resting tachycardia induced by RRS in both normotensive (P<0.05) and SHR (P<0.001) rats was mediated by an increase in cardiac sympathetic activity.

Conclusion: Present findings did not indicate an influence of hypertension in cardiovascular and neuroendocrine changes evoked chronic stress. However, data suggest a stress type-specific influence in cardiovascular function of both hypertensive and normotensive rats.

Financial support: FAPESP and PADC-FCF/UNESP.

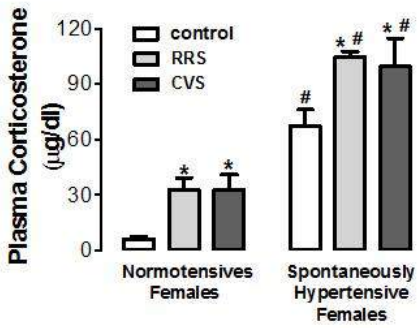

Figure: Plasma corticosterone concentration. The bars represent the mean±SEM. *P<0.05 vs respective control group, #P<0.05 vs respective male group. Two-way ANOVA followed by Bonferroni post-hoc test (n=6-7/group).

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Poster number: P-T051
Theme: The neurobiology of stress

Mineralocorticoid and glucocorticoid receptor binding to glucocorticoid target genes in the rat hippocampus after stress

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Glucocorticoid hormones (GCs), secreted after stress or during the circadian rise, act on the brain through binding to mineralocorticoid (MRs) and glucocorticoid receptors (GRs). After hormone binding and activation MRs and GRs bind to glucocorticoid response elements (GREs) within target genes (e.g. FK506-binding protein 5 (Fkbp5), serum/GC-regulated kinase 1 (Sgk1), Period 1 (Per1)) to evoke changes in gene transcription. Based on early hormone binding studies (Reul & de Kloet, Endocrinology 1985) it was thought that MRs and GRs exert a tonic and feedback/cognition-enhancing influence, respectively, on brain function. This concept has not, however, been investigated regarding MR and GR to GRE binding at the genomic level.

Male Wistar rats were exposed to stress and hippocampus tissue collected at various time points after stress or under baseline conditions for chromatin immuno-precipitation (ChIP) to assess MR and GR binding to GREs within target genes or for RNA analysis by qPCR.

Forced swimming, and the circadian rise in GCs, caused significant transient rises in Fkbp5, Sgk1 and Per1 hnRNA and mRNA levels. These changes were associated with substantially increased binding of both MRs and GRs to a specific GRE within intron 5 of Fkbp5 and to GREs within the Sgk1 and Per1 gene promoters. Despite generating distinct GC responses, novelty and restraint stress elicited similar MR and GR to GRE binding profiles as forced swimming. MR and GR Tandem ChIP provided strong evidence that these receptors bind as MR:GR heterodimers and GR:GR homodimers to Fkbp5 and Per1 GREs, whilst only bind as GR:GR homodimers to Sgk1 GREs after stress (Mifsud & Reul, PNAS 2016).

In summary, whilst the GR to GRE binding profile was expected based on earlier receptor binding studies, the low MR binding to GREs under baseline AM conditions was surprising given the high levels of MR occupancy shown previously. Different stressors resulted in similar GRE binding indicating that above a certain threshold responses are independent of GC levels. MR and GR to GRE

binding as well as their binding as homo- versus heterodimers is very GRE- and gene-dependent. Thus, GC action at the genomic level is highly complex with multiple layers of regulatory control.

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Poster number: P-T052
Theme: The neurobiology of stress

Salivary Cortisol as a Physiological Response to Stress on Musicians

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Performing complex music plays can cause stress and memory lapses with important impact on musician's presentation and careers.

Cortisol is one of the glucocorticoids regulated by the HPA axis considered as an indicator of the activity of this system in stress response. In its biologically active form it is a component of saliva and the majority remains unbound to proteins allowing to a convenient method of estimating serum cortisol levels which rise in response to stress independently of the circadian rhythms that regulate the secretion of this hormone.

In a pilot study using a salivary enzyme-linked immunosorbent assay a panel of musicians were evaluated in terms of stress by monitoring salivary cortisol in "normal" day life and under recitals.

Neuropsychological measures were also taken from each voluntary.

The effect of a stress mitigating intervention (a memory improving technique) was considered by comparing with musician group control. Despite individual variations that were not unneglectable and the role of possible confounding factors as gender circadian patterns, all requiring an extended sampling, the pilot study detected evidences of hormonal variation in response to recital stressor as higher cortisol levels were obtained for the recital days .

Considering the effect of a learning technique over stress in performance ("superlearning") two groups of piano classes were compared in three repeated evaluations the control group have no special learning training techniques to improve the play or to reduce stress. The control group however showed similar results that are consistent with higher stress levels which maybe lead to consider the superlearnig technique as a stronger stressor itself than music performance.

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Poster number: P-T053
Theme: The neurobiology of stress

Co-activation of the sympathetic and the parasympathetic nervous systems during heat stress

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During heat stress, sympathetic activity increases monotonically until the heat shock develops. Changes in parasympathetic activity are not described yet. To characterize the parasympathetic control of heart rate during heat stress, 4-months old male Wistar-Kyoto rats (n=8) were implanted with telemetric transmitters. Aortic blood pressure, ECG, core body temperature, and animal activity were monitored during exposure to hot (44°C) environment in a climatic chamber. Time-frequency analysis based on Wigner-Ville transform was used to estimate the high-frequency power of RR-interval variability (HFRRI) and low-frequency power of systolic pressure variability (LFSPV) in 2 s long intervals. Numerical values represent mean (standard deviation). After exposing rats to the heat stressor, core body temperature (Tc) remained stable for 2.9 (1) min and increased steadily thereafter. Heatstroke developed at Tc of 42.7 (0.2) °C. LFSPV, a surrogate measure of vascular sympathetic activity, rose from 4.2 (0.9) mmHg2 to a maximum of 14.3 (2.6) mmHg2 attained during heatstroke. Simultaneously, the pre-ejection time reduced from 42 (6) ms to 33 (3) ms indicating an increase in the cardiac sympathetic drive. HFRRI (a surrogate measure of the cardiac parasympathetic activity) augmented from baseline values of 3.4 (0.9) ms2 to 21.4 (6.8) ms2 at the beginning of the heat stress. The elevated parasympathetic activity was confirmed pharmacologically with heart rate and HFRRI response to the muscarinic blockade with atropine methyl nitrate. HFRRI

remained elevated until Tc reached 41.3 (0.3) °C and then decreased to 0.9 (0.1) ms2. Heart rate initially rose slowly (2.8 (1.2) bpm/min), but the speed of heart rate increase accelerated and reached values of 10.2 (3.4) bpm/min after the reduction of HFRRI. In conclusion, exposure to high ambient temperature co-activates the sympathetic and the parasympathetic nervous systems. While cardiac and vascular sympathetic activity progressively increased until heatstroke developed, cardiac parasympathetic activity was strongly elevated from the beginning of the heat stress but virtually abolished at core body temperatures above 41 °C. The decline in the cardiac parasympathetic activity was associated with the accelerated rise of heart rate.

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Poster number: P-T054
Theme: The neurobiology of stress

Circadian tryptophan hydroxylase expression in the dorsal and median raphe nuclei is altered by dysregulated glucocorticoid rhythms

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Stress-related psychiatric disorders are often characterized by dysregulated activity of both the hypothalamus-pituitary-adrenal axis (HPA axis) and the serotonergic system. Nonetheless, it's still unclear if the irregularities of the HPA axis are the cause or effect of the anomalies in the serotonergic system. We hypothesize that the activity of the HPA axis has an important role in the regulation of the rate limiting enzyme in the biosynthesis of serotonin Tryptophan hydroxylase (Tph2), and therefore in the serotonergic system. Three models have been used; 1) The natural circadian rhythm of glucocorticoids (GC); 2) Alteration of the GC rhythm by the administration of a synthetic GC methylprednisolone (MPL); and 3) Modification of GC activity by constant light exposure for 5 weeks. To evaluate the effects of these manipulations we used; a) Radioimmunoassays (RIA) to assess GC concentrations in plasma b) In situ Hybridization Histochemistry (ISHH) to evaluate changes in mRNA expression of Tph2 in the Dorsal Raphe (DR) and the Median Raphe (MnR). The results have shown the expected circadian GC rhythmicity in the control rats, suppressed endogenous GCs in the MPL treated rats, and hyperactive GC secretion in the constant light exposed rats. The ISHH dataset analyses have shown that Tph2 expression is profoundly altered in the DRV and the MnR after MPL treatment compared to normal control rats. In the DRV, Tph2 expression is lowest at 9am and greatest at 3pm in control rats. In contrast, the circadian rhythm of Tph2 expression is far less pronounced after MPL treatment. Throughout the MnR, the lowest Tph2 expression is observed at 9am and highest expression at 3pm in control rats and there is a striking increase observed at 6pm across a region of the MnR as a result of MPL treatment. The overall amplitude of Tph2 mRNA expression in both the DRV and MnR is generally much lower in the MPL treatment groups than in the controls, potentially indicating an overall down regulation of Tph2 mRNA levels as a result of chronic sGC treatment and the associated prolonged GR activity. This decrease in Tph2 might have significant implications for serotonin biosynthesis in the DR and MnR, which in turn would impact upon the serotonergic system and affective state.

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Poster number: P-T055
Theme: The neurobiology of stress

Effect of neuroticism on the CES functions

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Neuroticism is a personality trait which refers to inclination of negative affectivity. It has been proposed that high level neuroticism leads decreased activations in prefrontal cortices during dual task processing by impoverishing the cognitive resources in prefrontal cortices. However, neuroanatomical correlates of these activations in terms of central executive functions (CES) are unknown. To investigate for this, 15 high and 15 low neurotics were performed a PRP dual task with short (higher CES demand) and long (lower CES demand) stimuli onset asynchrony (SOA), while I assessed brain activity by means of functional magnetic resonance imaging (fMRI). Behavioural results showed high neurotics had lower performance (response times and error rates) in short SOA dual tasks than in the long SOA tasks. Imaging data showed that high neurotics showed decreased activations mainly in lateral prefrontal lobe (inferior and middle frontal gyrus) as the demand increase on the central executive system. In conclusion, high neuroticism leads lower behavioural performance and at the same time decreased activations in lateral prefrontal cortices as the demand increase on the central executive system.

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Poster number: P-T056
Theme: The neurobiology of stress

Effects of chronic social stress on 5-HT1A, 2A, and 2C receptor binding in mouse brain regions associated with reward processing

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Serotonin (5-HT), via its various receptors, each of which is expressed in discrete brain regions, modulates aversion and reward processing and is implicated in various psychopathologies including eating disorders and depression. In mice, chronic social stress in adulthood leads to increased food intake in the absence of weight gain but reduces effortful motivation to obtain gustatory reward [1]. The aim of this study was to investigate for stress effects on three 5-HT receptors, namely 1A, 2A and 2C, by quantifying their specific binding in some brain regions underlying reward processing: medial prefrontal cortex (mPFC), hippocampus (HIPP), amygdala (Amy), nucleus accumbens (NAcc), ventral tegmental area (VTA), dorsal raphe nucleus (DRN) and locus coeruleus (LC).

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Poster number: P-T057
Theme: The neurobiology of stress

Effects of maternal antioxidant treatment in mediating the outcomes of prenatal stress on the brain and behaviour

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Prenatal social stress (PSS) results in heightened anxiety behaviour in the adult male offspring, accompanied by increased gene expression for corticotrophin releasing hormone (CRH) in the central amygdala (CeA), and greater hypothalamo-pituitary-adrenal (HPA) axis responses to stress in the adult female offspring [1, 2]. This study aims to characterize if PSS has an effect on depressive-like behaviours, and whether maternal administration of an antioxidant can abrogate these abnormalities. The antioxidant, mitoquinone encased in nanoparticles (MitoQ-NP), does not cross the placental barrier and has previously been shown to prevent some of the effects of another paradigm of prenatal stress (hypoxic stress).

MitoQ-NP or saline was administered intravenously to pregnant dams on day 16 of gestation.
Dams were then left undisturbed or subjected to social stress (resident-intruder paradigm) on days
16-20. Male and female offspring were tested during adulthood on the light-dark box (LDB) and elevated plus maze (EPM) to assess anxiety-like behaviour, followed by the sucrose preference test (SPT) and forced swim test (FST) to assess depressive-like behaviour. After behaviour testing, brains were collected, frozen and sectioned for in situ hybridisation using radiolabelled probes for CRH mRNA. To a separate group of rats, blood samples were collected via an indwelling jugular vein cannula from adult female offspring to assess HPA axis activity before and after exposure to acute stress (30 min restraint).

PSS resulted in heightened anxiety-like behaviour in both the LDB and EPM in the adult male offspring. Maternal MitoQ-NP treatment prevented this anxious behaviour, and this was accompanied by the normalisation of CRH expression in the CeA. Neither the male or female PSS offspring exhibited a depressive-like phenotype in the FST or SPT compared with controls. Administration of maternal MitoQ-NP, however, decreased floating behaviour in male and female control and PSS offspring, indicating an anti-depressant effect. The corticosterone response to acute stress was prolonged in the PNS females compared with controls, and was not altered by MitoQ-NP treatment.

[1] Brunton PJ & Russell JA (2010) J Neuroendocrinol 22:258-71.
[2] Brunton PJ et al (2011) Stress 14:634-43.

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Poster number: P-T058
Theme: The neurobiology of stress

Behavioural and cortical pain responses in human infants are dissociable by their relationship to physiological stress

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Introduction: In adults, noxious stimulation evokes a cortical pain response and subjective pain report that are modulated by the level of physiological stress. The relationship between pain and stress is proposed to be a significant factor in individual variability of pain perception1. In newborn infants noxious stimulation evokes well-described pain behaviour, which is commonly used in place of pain report2 and nociceptive specific cortical activity (nociceptive Event Related Potential, nERP) as measured with EEG3. However, the effect of physiological stress levels upon infant cortical and behavioural pain measures is not known. Here, we investigate this by simultaneously measuring salivary cortisol, heart rate variability (HRV), nERP, and pain behaviour in neonates following a heel lance.
Method: 66 healthy neonates (mean GA 38.8 weeks; mean PNA 3.6 days) were studied during a clinically required heel lance. Ethical approval was given by the UK NRES and UCL/UCLH Joint Research Office.
Cortical activity, time locked to the heel lance, was recorded using EEG3. Salivary cortisol and ECG data for HRV calculation were collected before and after the procedure. Pain behaviour was scored using the Premature Infant Pain Profile (PIPP)2.
Results: The nERP amplitude was positively correlated with the PIPP following a heel lance (r=.36, p=.033). In addition, higher cortisol concentration and lower HRV, indicative of higher levels of physiological stress, were associated with larger nERP amplitude (r=.41, p=.029; r=-.42, p=.027). In contrast, PIPP was unrelated to the level of stress. Interestingly, the direct relationship between the nERP and PIPP was disrupted in babies that had a higher level of physiological stress (r=.27, n.s.).
Conclusion: The findings suggest that the cortical nociceptive response provides a more comprehensive measure of the pain experience of infants compared to pain behaviour as it also reflects their level of stress. Moreover, when infants are in a higher state of stress their behaviour in response to a lance is no longer an accurate reflection of the cortical pain processing.
References:

1. Vachon-Presseau et al. (2013). J Neurosci, 33: 6826–6833.
2. Stevens et al. (1996). Clin J Pain, 12: 13-22.
3. Fabrizi et al. (2011). Curr Biol, 21: 1552–1558.

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Poster number: P-T059
Theme: Neuronal, glial & cellular mechanisms

Involvement of GABAAr and NMDAr in the anticonvulsant actions of cannabidiol – studies in human cortex and rodent entorhinal cortex in vitro

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Phytocannabinoid derivatives of Cannabis Sativa are an exciting new class of anticonvulsants and one, cannabidiol (CBD), has displayed potent anticonvulsant properties in recent clinical trials in patients with two forms of childhood onset epilepsy. Here, we investigated the anticonvulsant effect of 30µM CBD using whole-cell patch clamp recording in Layer II of the medial entorhinal cortex of adolescent male status epilepticus experienced (SE) and age-matched control (AMC) Wistar rats (50-100g) in vitro. The Reduced Intensity Status Epilepticus (RISE) model of acquired epilepsy was used to induce epileptogenesis. Data were also collected from ex vivo human tissue (HT), resected in pediatric neurosurgery from patients with drug-refractory epilepsy. The effects of CBD on amplitude (pA) and inter-event intervals (IEIs) of spontaneous inhibitory post-synaptic currents (sIPSCs) were compared between SE and AMC rats. In SE rats, CBD significantly increased sIPSC amplitude (39.5 ± 4.4 to 52.5 ± 6.5 pA, P<0.0001) and decreased IEI (74.6 ± 15.3 to 62.3 ± 12.2 ms, P=0.02, n=5) while in AMC we saw a reduced effect (43.6 ± 17.3 to 52.6 ± 19.1 pA, P=0.099; IEI: 122.2 ± 28.7 to 147.8 ± 38.8 ms, P=0.16; n=6). Elucidation of the mechanism of action focused on GABAAR and NMDAR involvement. Using SE rats, 500nM flumazenil and 5µM ß-carboline-3-carboxylic acid-N-methylamide (ß-Carb) were used to inhibit benzodiazepine binding sites of GABAARs. NMDARs were inhibited competitively using 5µM D-AP-5 and non-competitively using 100nM MK801. Flumazenil addition caused a significant decrease in amplitude upon CBD addition (32.4 ± 12.8 to 21.9 ± 5.9 pA, P=0.024) and increased IEIs (93.2 ± 20.9 to 125.3 ± 42.5 ms, P=0.36; n=5). ß-Carb reduced the effects of CBD (37.0 ± 5.8 to 34.1 ±

2.2 pA, P=0.69; IEI: 72.9 ± 16.5 to 63.1 ± 13.5 ms, P=0.36; n=5). Inhibition of NMDARs by both drugs was sufficient to block the effects of CBD (AP-5: 31.1 ± 6.5 to 27.5 ± 6.4 pA, P=0.18; IEI: 121.7 ± 39.2 to 142.6 ± 49.6 ms, p=0.37; n=5) (MK801: 28.9 ± 4.2 to 30.0 ± 6.6 pA, P=0.96; IEI: 75.5 ± 24.6 to 85.2 ± 27.3 ms, P>0.9; n=6). Experiments in ex vivo HT trended towards similar results as those above. These data indicate the possible involvement of GABAARs and NMDARs in the anti-epileptic mechanism of CBD.

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Poster number: P-T060
Theme: Neuronal, glial & cellular mechanisms

Genetic regulation of a new stem cell niche in the adult hypothalamus: The Role of Fibroblast growth factor signalling

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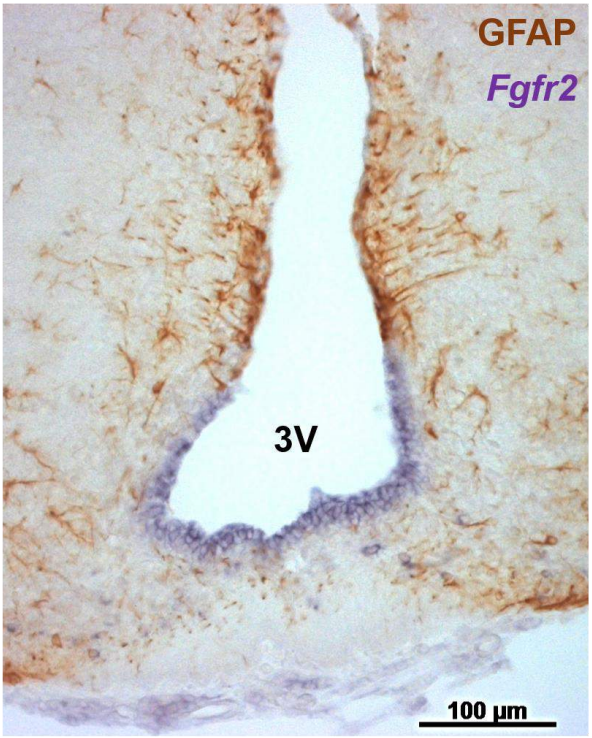
Throughout adult life, new neurons are generated in the hippocampal subgranular zone (SGZ) and the lateral subventricular zone (SVZ) of rodent brain. More recent studies show that the adult hypothalamus also harbours neural stem/progenitor cells (NSPCs) called tanycytes. Tanycytes populate the floor of the third ventricle and give rise to neurons that get integrated into appetite regulating centres. Although little is known about genetic regulators of postnatal hypothalamic neurogenesis, the fibroblast growth factor (FGF) system is emerging as an important candidate. However, the endogenous FGF/FGFR signalling partners in adult hypothalamic neurogenesis remain unknown. To identify these, we surveyed the expression of FGF ligands, their receptors as well as signalling modulators in the adult hypothalamus niche by reverse-transcriptase PCR, in situ hybridization, immunolabelling, and through the use of reporter mice. We find that distinct FGF family members as well as FGF signalling modulators such as Sproutys are expressed by tanycytes. Beta-klotho, a co-receptor mediating the effects of endocrine FGF ligands was also detected. These differential patterns of expression within the ependymal lining, the hypothalamic neurogenic niche as well as the hypothalamic parenchyma are indicative of multiple roles for FGFs within and outside the hypothalamic neurogenic niche. Targeted gain- and loss of function studies are underway to decipher the postulated functions assigned to FGF signalling in the hypothalamic neurogenic niche.



Mutually exclusive expression of GFAP and *Fgfr2* in alpha and beta tanycyte domains respectively.
In situ hybridization (*Fgfr2)* combined with immunohistochemistry (GFAP).
3V- third ventricle; GFAP – glial fibrillary acidic protein; *Fgfr2* – fibroblast growth factor receptor 2.

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Poster number: P-T061
Theme: Neuronal, glial & cellular mechanisms

The Role of External Tufted cells in activity-dependent plasticity of the olfactory bulb

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Neuronal plasticity allows networks to learn and adapt to the environment and change behaviour accordingly. The highly plastic olfactory bulb network serves as a good model to study plasticity. Olfactory bulb plasticity is viewed as primarily an interneuron phenomenon as these cells replenish throughout life and undergo activity-dependent plasticity. External tufted cells (ETC) are excitatory interneurons found in the glomerular layer of the olfactory bulb that are major modulators of olfactory sensory processing. However, surprisingly little is known about activity-dependent alterations in these neurons, though their location and monosynaptic connection to olfactory sensory neurons (OSNs) would suggest a role in adapting the network to environmental changes.
To understand whether these cells are important for adapting the olfactory network, ETC functional and structural characteristics were compared in control and 24 hour naris occluded mice. Whole-cell patch clamp recordings in acute olfactory bulb slices reveal that intrinsic excitability, assessed by multiple spiking properties, does not change with this manipulation. Additionally, ETC-characteristic spontaneous burst firing does not change in terms of number of spikes fired, or burst properties. Furthermore, neither single spike properties nor sag potential amplitude show significant differences after occlusion. However, when assessing synaptic properties, ETCs in occluded conditions have larger spontaneous long lasting depolarising currents, with no change in the frequency of their occurrence. We further investigated whether occlusion results in a change in the release probability at OSN synapses by recording from ETCs while stimulating OSN axons. We found that after occlusion the paired-pulse ratio (PPR) of these inputs decreases, suggestive of an increase in release probability at OSN synapses.
These alterations are indicative of adaptive plasticity in excitatory signaling in the olfactory bulb glomerular network. They may act to control the gain of information flow through the circuit, maintaining sensory performance in the face of external perturbations.

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Poster number: P-T062
Theme: Neuronal, glial & cellular mechanisms

Internodal length variability and myelination patterns in the developing mouse somatosensory cortex

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The importance of myelin in cognitive functioning has increasingly been implicated, and its loss or damage is known to be associated with several neurological and mental illnesses1. Our understanding of myelination patterns and characteristics during development, despite the clear significance of myelin, is still incomplete. Across species, white matter volume increases have been observed in development in several brain regions2,3,4. Notwithstanding, the exact nature of developmental myelination in rodent models such as mice is unclear. Therefore, we investigated the myelination pattern and internodal length in the developing mouse brain. Differential patterns of myelin distribution have been found in distinct layers of the mouse cortex5 and more specific features of myelin (such as internodal length and amount of internodes along axons) might potentially affect conduction speed. In the peripheral nervous system, a functional relationship between internodal distance and conduction speed has been demonstrated and internodal length increases throughout development6. We were therefore interested whether the same phenomenon occurs in the central nervous system (CNS). In order to investigate the myelin distribution in the somatosensory cortex and to measure the internodal length in this brain region, we used immunohistochemistry and high-resolution confocal imaging in animals during development (p0-p118), over regular time intervals. We found that cortical myelination started later than in the white matter and gradually increased in over time. Our preliminary findings suggest that instead of an average increase of the internodal length, the variability of internodal lengths increases during development in the CNS. This variability may suggest that developing neural circuits may be accompanied by characteristic, staged changes in myelination.

References
1 Baumann, N. & Pham-Dinh, D. (2001) Physiol. Rev. 81:871-927
2 Barnea-Goraly et al. (2005) Cerebral Cortex 15:1848-1854
3 Imperati et al. (2011) PLoS ONE 6(8): e23437
4 Hamano, K., Iwasaki, N., Takeya, T. & Takita, H. (1996) Developmental Brain Research 93:18-22
5 Tomassy et al. (2014) Science 344:319-324
6 Wu, L.N., Williams, A., Delaney, A., Sherman, D.L. & Brophy, P.J. (2012) Current Biology 22:1957-1961.

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Poster number: P-T063
Theme: Neuronal, glial & cellular mechanisms

An investigation into the contribution of TRAKs, mediators of neuronal mitochondrial transport, to the excitability of adult pyramidal CA1 neurons

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Mitochondrial movement along microtubules using molecular motors, kinesin and dynein ensures adequate provision of ATP and Ca2+ buffering during neuronal activity. Previous work established that the kinesin adaptor proteins, TRAK1 and TRAK2, play an important role in mitochondrial transport in cultured neurons. They link mitochondria to kinesin via a TRAK acceptor protein in the mitochondrial outer membrane, the Rho GTPase, Miro. In addition, TRAKs associate with the post-translational modification enzyme, O-linked N-acetylglucosamine transferase (OGT), to form quaternary mitochondrial trafficking complexes. Miro acts as a Ca2+ sensor and OGT as a glucose sensor. Thus both aid localization of mitochondria to specific neuronal regions where Ca2+ buffering and energy are required.

Down-regulation of TRAK1 or TRAK2 utilising shRNAs as well as dissociation of TRAK proteins from the quaternary complex by a TRAK2 dominant negative (DN) impaired mitochondrial transport in cultured hippocampal neurons1. It is known that in these neurons, TRAK2 predominantly mediates mitochondrial transport in dendrites whereas TRAK1 mediates axonal transport2.

The effects of compromising TRAK function on the activity of mature hippocampal neurons are unknown. Here, we have investigated this by stereotaxically injecting an adeno-associated virus 2 (AAV2) vector containing a TRAK2 DN construct or an appropriate control into the CA1 hippocampal region of adult rats. Three weeks post-surgery, brain slices were prepared and electrophysiological recordings made from infected CA1 pyramidal neurons to determine the intrinsic membrane properties, action potential firing rates and evoked excitatory post-synaptic potential kinetics and integration. Neurons were also filled with neurobiotin during the recordings and post-hoc analysis was carried out to determine cell morphology.

These studies will aid our understanding of the contribution of TRAK function to normal neuronal activity in the adult brain.

Supported by BBSRC (UK).

1. Brickley, K and Stephenson, FA (2011) J. Biol. Chem. 286, 18079.
2. Loss, O and Stephenson, FA (2015), J. Neurosci. Res., 93, 1056.

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Poster number: P-T064
Theme: Neuronal, glial & cellular mechanisms

The role of Wnt signalling in AMPA receptor trafficking and synaptic plasticity

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Structural and functional plasticity at glutamatergic synapses are critical for learning and memory. Long-term potentiation (LTP), induces spine growth and synaptic localisation of major excitatory glutamate AMPA receptors (AMPARs), thus enhancing synaptic strength. Glutamate initiates these processes, but the contribution from extracellular modulators is not fully understood. Wnt secreted proteins are imperative for synapse formation but their impact on LTP mediated spine plasticity and AMPAR localisation is unknown. Using a multidisciplinary approach that combines cellular biology and electrophysiology techniques, we show that LTP induction rapidly increases Wnt7a/b at spines. Importantly, blockade of endogenous Wnts or loss of Frizzled-7 (Fz7) receptor function, a receptor for Wnt7a, impairs LTP-mediated spine growth and synaptic AMPAR localization. Wnt7a rapidly promotes the

synaptic recruitment and trapping of AMPARs followed by an increase in spine growth. Wnt7a achieves this through CaMKII-dependent loss of Ras-GTPase SynGAP from spines and activation of the Ras-ERK pathway. Thus, our studies identify Wnts, through Fz7, as key initiators of LTP-mediated synaptic accumulation of AMPARs and spine plasticity.

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Poster number: P-T065
Theme: Neuronal, glial & cellular mechanisms

Postnatal Development of the Action Potential Waveform

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Over the first two weeks of life, neurons in the neonatal mouse undergo enormous change, migrating, maturing, and adapting in electrical activity, morphology and synaptic connectivity. Action potentials, the primary indicator of neuronal activity, drive the patterns of synaptic transmission that underpin neuronal communication and control calcium influx that shapes patterns of gene expression. As such, changes to the waveform of the action potential over the course of development will have potentially a wide-ranging and profound influence on neuronal structure and function. We examine changes to the postnatal action potential waveform via whole cell current clamp electrophysiology in layer 4 stellate cells of the somatosensory cortex between postnatal days (P)3 and (P)11. We show that postnatal maturation is associated with large increases in the height and speed of individual action potentials. Using Hodgkin-Huxley style computational models, we attempt to characterise the changing ionic mechanisms in the neurons. We develop a computationally efficient analytical method of multiple-parameter optimisation of this model of active neuron dynamics, prior to fitting to data. The changing morphology and its impact on the intrinsic electrical properties of the developing neuron is also considered, with the capacitance of the cell membrane hypothesised to change with the increasing size and shape of the soma and dendritic arbour. Current clamp recordings of the passive voltage across the cell membrane are analysed using a two compartment model of exponential decay. Interestingly, a fast voltage decay component present in some cells may be attributed to the presence of gap junctions which could influence these passive currents, and have implications for the regulation of neural network development. Injection of dye into the patched cell during whole cell recording, followed by confocal imaging, is used to detect the presence of surrounding gap-junction-coupled neurons. We aim to compare this to the intrinsic electrical properties of the cell at different stages of development, to produce a complete picture of the changing biophysical nature of the neuronal action potential as the neuron approaches maturity.

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Poster number: P-T066
Theme: Neuronal, glial & cellular mechanisms

Presynaptic muscarinic receptors modulate the feedforward Temporoammonic microcircuit in the hippocampus

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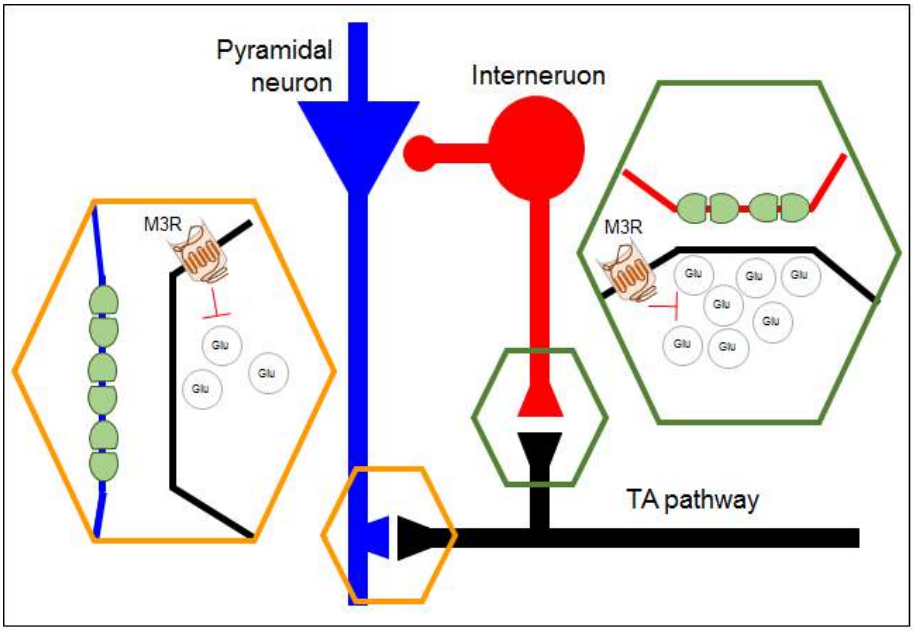
The release of acetylcholine in the hippocampus during awake behaviour is important for encoding memory. Within the hippocampal network, acetylcholine has diverse effects: it increases neuronal excitability, controls synaptic strength and regulates the induction of synaptic plasticity. However, these effects are not ubiquitous and instead are exhibited at individual synapses within the network. The Temporoammonic (TA) pathway carries spatial information from grid cells in entorhinal cortex layer III to CA1 hippocampal place cells synapsing onto the distal dendrites. It is not currently known how acetylcholine regulates synaptic transmission in the temporoammonic pathway or which acetylcholine receptors mediate this regulation. To determine how acetylcholine regulates the TA pathway we made whole cell patch clamp recordings from CA1 pyramidal neurons or selected subset of interneurons in acute hippocampal sagittal slices from adult mice. Electrical stimulation in the Stratum Lacunosum Moleculare was used to isolate monosynaptic excitatory postsynaptic currents (EPSC) or disynaptic inhibitory postsynaptic currents (IPSC). The acetylcholine receptor agonist carbachol (CCh 10 ?M) reduced both excitatory and inhibitory synaptic responses and increased paired-pulse ratio for excitatory responses, indicating a presynaptic locus of action. Specific pharmacological intervention showed that M3 receptor antagonist or genetic deletion of this receptors, blocked CCh induced reduction of synaptic probability of release. Furthermore, we revealed that PV+ Interneurons are feedforward upon TA pathway stimulation, whose excitatory inputs are inhibited by the activation of M3 receptors. Excitatory and inhibitory responses at pyramidal neurons were similarly reduced by CCh

but the increase in paired pulse ratio for excitatory drive produced a facilitation of excitatory-inhibitory balance in response to repetitive stimulation. In addition, CCh produced an increase in the number of spikes in the CA1 pyramidal neurons when TA synapses were repeatedly stimulated over a range of frequencies. We conclude that acetylcholine modulates the temporoammonic pathway by presynaptically located M3 muscarinic receptors.



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Poster number: P-T067
Theme: Neuronal, glial & cellular mechanisms

Role of CSF1 vs. IL-34 in the control of CSF1R function in microglia in vitro

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The expansion and activation of microglia, the brain's resident population of myeloid cells, is a hallmark of many neurodegenerative diseases including Alzheimer's disease and prion disease. Colony stimulating factor 1 receptor (CSF1R) is critically involved in regulating proliferation of microglia both in the healthy and diseased brain. CSF1R can be activated by two independent ligands, CSF1 and interleukin (IL-) 34. Ligand binding to the receptor leads to tyrosine kinase phosphorylation and activation of intracellular signalling pathways involved in survival, proliferation and differentiation of microglia.

In this project, we aim to obtain a clear understanding of the effect of CSF1 vs. IL-34 on CSF1R activation in microglia, with a specific focus on potential differences in the activation pattern between the two ligands. Using a murine microglial cell line (N13) and primary murine microglia, we observed a rapid and transient phosphorylation of CSF1R after stimulation with CSF1 or IL-34. Likewise, CSF1R downstream pathways ERK1/2, AKT, SAPK/JNK and p38 were activated upon receptor phosphorylation. Expression of genes implicated in proliferation and inflammation were modulated after CSF1 or IL-34 stimulation in a concentration-dependent manner. Finally, primary microglia demonstrated a pronounced increase in proliferation after CSF1R activation.

In consideration of the inflammatory response observed after treatment with CSF1R ligands, we aimed to determine whether "priming" with CSF1 or IL-34 affects the expression of inflammatory genes in microglia in response to an inflammatory stimulus (i.e. LPS). We observed a reduction in the expression of pro-inflammatory markers after short-term priming of CSF1R, which is reversed to baseline levels when cells were primed for a longer period of time.

These results provide insight into the kinetics of CSF1R activation by CSF1 vs. IL-34 in microglia cells and establish the basis to further study the differential role of both ligands in CSF1R function.

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Poster number: P-T068
Theme: Neuronal, glial & cellular mechanisms

The excitatory neurotransmitter glutamate influences the DNA damage repair in in vitro differentiated murine neurons

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The ability of neural stem cells to self-renewal and to differentiate into neurons, oligodendrocytes and astrocytes is essential for a balanced neurogenesis in adult brains. Low-dose gamma irradiation endangers genomic stability in these cells by inducing DNA double-strand breaks (DSBs). Particularly, the immature neural stem cells are radiosensitive (Katsura et al. 2015, Saha et al. 2014). However, NSCs have two main repair ways to handle DSBs. On the one hand, there is homologous recombination which depends on a sister chromatid as repair template and is therefore only available in late S and G2 Phase. On the other hand, there is NHEJ (non-homologous end-joining) which includes the repair protein 53BP1. NHEJ is active throughout the cell cycle and consequently available in mature cells. It is little known about repair mechanisms in immature and mature neural cells and the consequences of unrepaired double strand breaks, so we irradiated murine stem cells (J1-NSCs) and focused on the NHEJ repair kinetics. Simultaneously, we differentiated the NSCs under specific culture conditions to their descendants (neurons, astrocytes and oligodendrocytes) and irradiated them as well. As expected, we see more 53BP1-Foci (indicator for DSBs) after irradiation in the radiosensitive neural stem cells compared to the descendants. Interestingly, the 53BP1-Foci quantity and the repair kinetics of astrocytes and neurons were different. We hypothesize that DSB repair in neurons is regulated by glutamate signaling through the N-Methyl-D-aspartate (NMDA) receptor (Yang et al. 2011). Our results indicate a connection between treatment with 30 µM glutamate and 53BP1-Foci formation in neurons. Moreover, this effect is inhibited by treatment with MK-801, an antagonist of NMDAR. Overnight treatment with glutamate affects the repair kinetics of neurons after low-dose irradiation, in a positive manner. Glutamate treatment neither induces 53BP1-Foci, nor has positive effects on the repair kinetics of astrocytes. We suppose that the excitatory neurotransmitter glutamate exclusively stimulates neurons via NMDAR activation. Our future experiments include the investigation of specific NMDAR subunit compositions in neurons and glial cells, to figure out the subunit influence on DSB repair.

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Poster number: P-T069
Theme: Neuronal, glial & cellular mechanisms

Glutamate NMDA, Dopamine D1 and Histamine H3 receptors form heterotrimeric complexes in brain

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Most evidence indicates that G protein-coupled receptors form heteromers between them and with other receptors. By allosteric mechanisms, them acquire a multiplicity of unique pharmacological and functional properties. Recently, we discovered that dopamine D1 receptors (D1R) and histamine H3 receptors (H3R) form heteromers through which H3R ligands can inhibit D1R function. D1Rs also physically interact and modulate ionotropic glutamate NMDA receptors (NMDAR). In the present work, we investigated if NMDAR, D1R and H3R form a heterotrimeric complex in brain.

The heteromer expression was studied in slices from both rat and mouse brain cortex by co-immunoprecipitation (Co-IP) and proximity ligation assays (PLA). The ability of D1R and H3R to interact with NMDAR in transfected HEK cells was analyzed by bioluminescence resonance energy transfer (BRET) with bimolecular fluorescence complementation (BiFC) experiments. Heteromer properties were studied by analyzing ERK1/2 phosphorylation and cell death in cortical slices.

Endogenous D1R-H3R heteromers were detected in rat and mouse cortical slices, where H3R ligands decreased D1R signaling (ERK1/2 pathway) and were also able to block the cell death induced by overstimulation of either D1R or NMDAR. By BRET experiments in transfected HEK cells, we demonstrated that both D1R and H3R form heteromers with NMDAR subunit 1A in the presence of subunit 2B. D1R-H3R-NMDAR heteromers were detected by BRET with BiFC. The expression of endogenous D1R-H3R-NMDAR heteromers were observed in rat and mouse cortex by PLA.

Many systems, including the glutamatergic and dopaminergic, are involved in neurodegeneration. Our innovative finding is that D1R, H3R and NMDAR form heteromers that may be a point of intervention for cognitive disorders in neurodegeneration.

Our results point out that D1R-H3R-NMDAR heteromers are expressed in brain cortex and a complex interaction exists between protomers in the heteromer, where H3R ligands act as a “molecular brake” for D1R and NMDAR signaling.

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Poster number: P-T070
Theme: Neuronal, glial & cellular mechanisms

A simplified and efficient method for the generation of early OPC and OPC from mouse embryonic stem cell-derived neural stem cells

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Introduction: Therapies to promote the differentiation of oligodendrocyte precursor cells (OPC) and boost myelin repair are lacking. In vitro culture systems are useful tools for the discovery of myelin repair treatments as they permit high-content screening of compounds in assays of OPC differentiation. Typically OPCs are derived from primary mixed glial cultures using expensive immunopanning methods, or complicated shaking procedures. Here we report a simplified and efficient protocol that generates early OPCs and later stage OPC from embryonic stem (ES) cell-derived neural stem (NS) cells. We also establish a simple protocol for OPC isolation from mixed glial cells derived from NS cells.

Methods: NS were cultured in serum-free media supplemented with growth factors including basic fibroblast growth factor (FGF2), Insulin-like growth factor 1 (IGF1) and platelet-derived growth factor (PDGF-AA). This culture condition converted NS cells into a population of early OPCs, which were easily distinguished by their different physical properties e.g. bi- and multi-process morphologies. Early OPC could then be used to generate mixed glial cultures, with OPCs adhered onto a layer of astrocytes. OPCs exhibited distinct diameters compared to astrocytes and so were easily isolated from the mixed cultures by cell straining. qPCR for marker genes was used to confirm the generation of early OPC (Nkx2.2), and OPC (NG2, PDGFRalpha), with results compared against primary OPC obtained from postnatal brain tissues. Also, cell diameters of the different cell types were measured to provide a simple way to predict the purity of each cell fraction.

Results and conclusion: Gene expression analyses showed that early OPC had a greater level of Nkx2.2 compared to OPC, while OPC expressed greater levels of the OPC marker genes NG2 and PDFRalpha. Cell diameter measurements further suggest that the simple protocol we established could isolate homogeneous cell population from mixed glial cells, demonstrating that we can generate early OPCs and OPCs from ES cell-derived NS cells, and that this simple protocol could isolate OPCs from mixed glial cells without complicated and costly steps such as overnight shaking or immunopanning.

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Poster number: P-T071
Theme: Neuronal, glial & cellular mechanisms

The expression of the chloride co-transporters NKCC1 and KCC2 is reversed in the penumbra following photothrombotic stroke in mice

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Stroke is one of the major causes of death and disability worldwide. The harm caused by the interruption of blood flow to the brain unfolds in the subsequent hours and days, so it is critical to identify new therapeutic targets that could reduce neuronal death associated with the spread of the damage. The area that surrounds the infarcted core is the location of the continuing damage that takes place hours and days following an insult, an is referred to as the penumbra. The expression of the chloride co-transporters, NKCC1 and KCC2, mediators of the GABAergic response, was assessed following hypoxia in differentiated PC12 and NT2 neuronal-like cells and in a photothrombotic model of stroke in mice. Differentiated PC12 and NT2 cells were exposed to hypoxia (1% oxygen) for 8 hours in a hypoxic modular chamber before gene and protein expression was analysed by qPCR and immunoblotting. Following hypoxia, the expression of KCC2 was significantly decreased at both the transcript and protein level whereas NKCC1 expression remained unmodified. In the in vivo model, the development of the penumbra in the days following injury was assessed with the specific markers HSP70 and GFAP. Two distinct areas were identified, the penumbra up to 200 m from the ischaemic core

and a glial migration zone up to 400 m. In the penumbra, a significant neuronal loss was observed up to 5 days following the insult. Our results show an increase in the number of neurons expressing NKCC1 in the penumbra up to 5 days following the insult when compared to the contralateral hemisphere. On the contrary, KCC2 positive cells were dramatically decreased in this area. Mice were treated with bumetanide and CLP257, an NKCC1 antagonist and a KCC2 agonist respectively. Neuronal loss was significantly reduced 3 and 5 days following the insult in the penumbra following bumetanide treatment. The reversal on NKCC1 and KCC2 might contribute to the excitotoxic damage that promotes the development of the penumbra in the days following an ischaemic event by interrupting or even reversing GABAergic mediated inhibition. Our results show how treatments targeting chloride co-transporters might represent a novel strategy to reduce the damage associated with stroke.

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Poster number: P-T072
Theme: Neuronal, glial & cellular mechanisms

A new form of hippocampal LTP mediated by kainate receptors

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Located on both pre- and postsynaptic membranes, kainate receptors (KARs) perform various distinct roles in modulating neuronal and synaptic excitability. Further, KARs participate in the regulation of neuronal network activity and are involved in processes ranging from neuronal development and differentiation to neurodegeneration and neuronal cell death. An important property of pre- and postsynaptic KARs is that, in addition to direct ionotropic signalling, they can also signal through the activation of G proteins 1. By utilizing the metabotropic signalling pathway via PKC activation, KARs mediate both presynaptic (facilitation of glutamate release and down-regulation of GABA release 1,2 and postsynaptic actions (inhibition of afterhyperpolarisation current I(sAHP), 3,4.

Aims: To characterize the mechanism of KAR-mediated postsynaptic LTP in the hippocampus.

Methods: We used molecular biology tools, high resolution and live cell imaging, as well as electrophysiological (whole-cell patch-clamp, as well as field recording).

Results: We have characterized a novel, physiologically relevant NMDA receptor-independent mechanism that drives increased AMPA receptor recycling and results in LTP. The process is mediated by the metabotropic action of kainate receptors and requires activation of G-protein, protein kinase C and phospholipase C. In addition, the structural plasticity occurring as a result of KAR-dependent LTP shares the same properties like that of classical LTP and is manifested by: recruitment of recycling endosomes to spines, enhanced synaptic recycling, increased AMPAR surface expression and structural changes in spines, including their increased growth and maturation.

Conclusions: We have characterized a previously unsuspected role of postsynaptic kainate receptors in the induction of functional and structural plasticity in the hippocampus.

References:
1 Neuron (1998) 20:1211-18.
2 Neuron (2003) 39:543-53.
3 Neuron (2002) 34:107-14.
4 The Journal of Physiology (2005) 562:199-203.

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Poster number: P-T073
Theme: Neuronal, glial & cellular mechanisms

An investigation in to the role of the putative cannabinoid receptor GPR55 in in vitro models of neuroinflammation and neurodegeneration

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Neurodegenerative conditions such as Alzheimer's disease (AD) are associated with neuronal loss and cognitive decline. To date treatments have largely focused on symptomatic management and only in recent years has this focus shifted to therapeutically tackling disease progression. A therapeutic approach that can halt the actions of AD is therefore attractive as it will be a potential strategy to impede disease progression.
The orphan G-protein coupled receptor GPR55 is responsive to cannabinoids and is widely expressed in the neurons and glia of the brain. The suggested endogenous ligand for GPR55, L-α-lysophosphatidylinositol (LPI), exerts microglia-dependent neuroprotection after excitotoxic lesion (Kallendrusch et al., 2013), suggesting that GPR55 may have a regulatory role in neuroinflammation and neurodegeneration. This makes GPR55 an attractive therapeutic target for conditions such as AD. The present study aims to examine the role of GPR55 and its signalling pathways in the regulation of neuroinflammation and neuronal cell death using in vitro models.
Cultured primary rat cortical neurons were treated with LPI (1 µM & 10 µM). LPI-induced signalling effects were assessed using phospho-cAMP element binding protein (pCREB) immunocytochemical staining and confocal microscopy and imaging of intracellular calcium responses. LPI induced CREB phosphorylation in a concentration- and time-dependent manner. LPI (10 µM) induced calcium responses. Cortical neurons were treated with LPI (1 µM & 10 µM) in the presence or absence of the AD pathological hallmark, Aβ, for 72 hours. The conditioned medium was then applied to the BV2 microglial cell line and the subsequent migration of BV2 cells was assessed using a Boyden chamber assay. Microglial migration did not increase upon exposure to medium taken from neurons conditioned with LPI (10 µM), whereas LPI (1 µM) increased levels of migration compared to control cells. Neuronal apoptosis was assessed by active caspase-3 immunocytochemistry. LPI (10 µM) significantly downregulated neuronal apoptosis evoked by Aβ and glutamate. This study suggests that LPI can confer a neuroprotective effect and demonstrates a possible role for GPR55 in the regulation of gene expression, microglial migration and neuronal apoptosis.

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Poster number: P-T074
Theme: Neuronal, glial & cellular mechanisms

Characterising the nature and mechanism of the CaV2.2-α2δ interaction

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Neuronal CaV channels are essential mediators of synaptic transmission, mediate the entry of extracellular Ca2+ at presynaptic terminals necessary for neurotransmitter release. N-type channels are implicated in a number of neuropathies including epilepsy and neuropathic pain; while the auxiliary α2δ subunit is the target of the antiepileptic drugs, Gabapentin and Pregabalin. The present study examines the interplay between N-type channels and the α2δ subunits which play an important role in CaVα1 trafficking and enhancement of macroscopic Ca¬V currents. Through confocal microscopy and patch-clamp recordings, we provide evidence that α2δ-1 enhances CaV2.2 plasma membrane expression through rab11a-dependent recycling. However, α2δ-3 has only a modest effect on CaV2.2 membrane expression and traffics in a rab11-independent manner. In addition, both α2δ-1 and α2δ-3 were seen to increase the expression of CaV2.2 in the processes of cultured hippocampal neurons; this effect was ablated by coexpression of the dominant negative Rab11a (S25N) mutant only when α2δ-1 was present. Interestingly, in neuro2A cells α2δ-1 and α2δ-3 both produce a comparable increase in total CaV2.2 expression, despite substantial differences in CaV2.2 surface expression. Together, our data suggests that α2δ-enhanced CaV current density may only partly relate to changes in CaV membrane expression. These findings could have significant implications for the development α2δ-targeted therapies for the treatment of CaV-associated neuropathies.

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Poster number: P-T075
Theme: Neuronal, glial & cellular mechanisms

Subcellular Localisation of Phosphorylated GluA1 Subunits

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Long term potentiation (LTP) is a molecular substrate of memory consolidation. One key mechanism underlying LTP is phosphorylation of AMPA receptor subunits, a process that can affect both receptor function and location. For example, phosphorylation of GluA1 subunits at Ser845 leads to trafficking of AMPA receptors to the synaptic cleft to strengthen synaptic connections [1, 2].

We are interested in the plasticity changes involved in addiction. Risk of relapse back to drug-taking in abstinent addicts persists long after drug-taking has ceased. Changes in synaptic strength in the brain contribute to this, as emotional and environmental cues become associated with drug-taking and trigger cravings [3].

The overall aim of this study was to examine synaptic plasticity changes following expression of addiction-related behaviour in rodents. cFos-GFP transgenic mice [4] underwent morphine-primed conditioned place preference and reinstatement. Following reinstatement, animals' brains were perfusion-fixed, sliced and GluA1 and phosphorylated GluA1 subunits at Ser845 in the hippocampus were examined by immunohistochemistry. The GluA1 subunits were largely expressed in the dendrites of neurons. Surprisingly, the majority of the Ser845-phosphorylated subunits were localised on the somas of pyramidal neurons, an observation which has not yet been reported. In LTP, the GluA1 subunits are thought to be phosphorylated in the post-synaptic terminal to trigger the trafficking of further AMPA receptors to the synapse, therefore their localisation in the cell bodies is unexpected. Further investigation into the relevance of this distribution is required for the better understanding of molecular mechanisms underlying motivational behaviour.

References:
1. Lee HK et al (2003) Cell 112:631-43
2. Henley JM & Wilkinson KA (2013) Dialogues Clin Neurosci 15:11-27
3. Korpi ER et al (2015) Pharmacol Rev 67:872-1004
4. Barth AL (2004) J Neurosci 24:6466-75.

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Poster number: P-T076
Theme: Neuronal, glial & cellular mechanisms

The initiation and propagation of ventral to dorsal medial entorhinal cortex epileptiform activity is reduced by an inhibitory gradient

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Epilepsy is a chronic disorder of the brain characterised by recurrent seizures. 1-2 % of the world's population are affected, with many sufferers developing resistance to drug therapy. Temporal lobe epilepsy (TLE) is the most common form of human epilepsy, in which the site of seizure initiation occurs in temporal lobe structures such as the entorhinal cortex (EC). In this study we examined the propagation of pharmacologically induced ictal-like epileptiform activity along the dorso-ventral axis of the medial EC (mEC). All procedures were in accordance with current UK Home Office regulations. 400 µm parasagittal slices were prepared from male C57BL/6 mice (3-6 month) and perfused (3-4 ml.min-1) with artificial cerebrospinal fluid. Recordings were made from layer II of the mEC using a 16-channel silicon probe consisting of 16 individual shanks (55 µm wide, 100 µm apart), with a single electrode contact point at the end of each shank. Application of 100 µM 4-aminopyridine (4-AP) to the perfusing ACSF resulted in the initiation and propagation of ictal activity from the ventral to dorsal end of the mEC at a speed of 197 ± 24 µm.s-1 SEM (n=12 slices, R2=0.44). Addition of the GABAA receptor positive allosteric modulator diazepam (30 µM) significantly decreased the speed of ictal propagation from 148 ± 23 µm.s-1 to 65 ± 14 µm.s-1 ($P<0.001$, n=6 slices, paired Student's t-test). Addition of the GABAA receptor inverse agonist Ro 19-4603 (10 nM) significantly increased the speed of ictal propagation from 170 ± 45 µm.s-1 to 1273 ± 117 µm.s-1 ($P<0.001$, n=6 slices, paired Student's t- test). This demonstrates that the relatively slow propagation of ictal activity across the mEC is controlled by GABAergic synaptic transmission. The initiation of ictal activity at the ventral pole of the mEC likely occurs due

to 1) the lower inhibitory tone and 2) the higher intrinsic excitability of individual stellate cells in this region cf. the dorsal mEC. This novel approach to understanding the underlying mechanisms involved in epileptiform activity in the mEC offers an in vitro model in which to probe antiepileptic drugs for the treatment of TLE.

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Poster number: P-T077
Theme: Neuronal, glial & cellular mechanisms

Identification of the types and location of transmembrane AMPAR regulatory proteins expressed in neurons of the mouse retina

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In excitatory pathways through the retina – from photoreceptors to ganglion cells –glutamate acts as a fast synaptic transmitter, activating predominantly AMPA-type receptors (AMPARs) in primary retinal neurons. Within the retina AMPAR subunits are differentially expressed with respect to cell type and ontogenetic period, but the auxiliary subunits responsible for regulating AMPAR trafficking and function remain unknown.
Transmembrane AMPAR regulatory proteins (TARPs; γ-2, -3, -4, -5, -7 and -8) are the best understood of the known AMPAR auxiliary subunits. In most brain regions TARPs are differentially distributed within neuronal and glial populations and play distinct roles in shaping synaptic transmission. We sought to identify which TARPs are expressed in retinal neurons, with the aim of determining their precise synaptic location and cellular distribution. Using Western blot of wild-type retinal protein, we detected expression of TARPs γ-2, -3, and -5. Using antibody labelling and immunofluorescence, we analysed TARP expression and cell-type localization in retinal cryosections. We found γ-2 (stargazin) to have a punctate pattern of expression in both the outer plexiform layer (OPL), where photoreceptors contact bipolar and horizontal cells, and inner plexiform layers (IPL), where bipolar and amacrine cells contact ganglion cells. These puncta co-localized with postsynaptic markers and AMPAR subunits suggesting a synaptic location. Additionally, we found labelling for γ-3 in cell bodies and dendrites within the OPL and in large cell bodies of the ganglion cell layer. These locations indicate that γ-3 is likely expressed in Off bipolar cells and ganglion cells. Finally, we identified γ-5 expression in the IPL only. By performing double- and triple labelling of fixed whole-mounted retinas and retinal cultures, we identified horizontal cells, Off bipolar cells and several populations of amacrine and ganglion cells that express, either singly or together, TARPs γ-2, -3, and -5.

Our data provide the first detailed characterization of the localization of TARP proteins in the retina. The specific expression patterns are consistent with a role for these proteins in regulating AMPARs at retinal synapses.
Acknowledgements: Supported by the MRC (MR/J002976/1).

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Poster number: P-T078
Theme: Neuronal, glial & cellular mechanisms

In vivo two-photon imaging of mitochondrial localisation during structural synaptic plasticity in the mouse somatosensory cortex

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Novel sensory experiences are encoded by changes in cortical neuronal networks (Holtmaat and Svoboda 2009). This experience-dependent plasticity is driven in part by structural changes at the synaptic level. It is known that, in the adult mammalian brain, a small but significant number of synapses are constantly removed and replaced. However, little is known about the subcellular processes that control synaptic turnover. Indeed, within the same axon a transient synapse can appear and disappear alongside a highly stable one (De Paola et al. 2010). This raises the question of what molecular players inside the pre- or postsynapse contribute to the stability of that synapse. Mitochondria have extensively been shown to be vital to presynaptic neurotransmission (Vos et al. 2010), we have therefore studied mitochondrial localisation at presynaptic boutons and their influence on structural synaptic plasticity in vivo. We used an AAV2/1 expressing a mitochondrially-targeted tagRFP and cytosolic EGFP to label axons projecting to the mouse somatosensory cortex. We imaged the turnover of axonal boutons and mitochondrial localisation longitudinally by two-photon microscopy through a cranial window. We show that the pattern of mitochondrial localisation in these axons changed over a period of days, with mitochondria preferentially localising to presynaptic boutons. The stability of presynaptic boutons was much

greater than that of mitochondrial localisation, however there were some sites where mitochondria were persistently found. Analysing the subcellular coordination of mitochondrial and synaptic turnover over time was used to establish the relationship between mitochondrial localisation and presynaptic bouton stability.

Holtmaat, A., Svoboda, K., (2009) Experience-dependent structural synaptic plasticity in the mammalian brain. Nat. Rev. Neurosci.
De Paola, V., Holtmaat, A., Knott, G., Song, S., Wilbrecht, L., Caroni, P., Svoboda, K., (2006) Cell Type-Specific Structural Plasticity of Axonal Branches and Boutons in the Adult Neocortex. Neuron.
Vos, M., Lauwers, E., Verstreken, P., (2010) Synaptic mitochondria in synaptic transmission and organization of vesicle pools in health and disease. Front. Syn. Neurosci.

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Poster number: P-T079
Theme: Neuronal, glial & cellular mechanisms

Expression of functional Nociceptin/Orphanin FQ (NOP) receptor on glia

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Glia are the major cellular components of the central nervous system (CNS) that when activated play important roles in inflammation, neuropathic pain and opioid tolerance (Giaume et al., 2007). In this study we determine the expression and function of the non-classical Nociceptin/Orphanin FQ (NOP) opioid receptor, shown to have important roles in pain processing and opioid tolerance (Lambert, 2008), in a variety of glial cell types.

Methods
Using 1321N1 human astrocytes, MO3.13 human oligodendrocytes, HOG human oligodendrocytes and EOC-20 mouse microglia (De Vries and Boullerne, 2010), a series of in vitro assays including quantitative PCR (qPCR), [leucyl-3H] N/OFQ saturation binding and scratch wound healing/cell migration were performed. We investigated: (1) the presence of mRNA encoding for NOP opioid receptor (2) NOP receptor expression and (3) functional activity of the expressed receptor.

Results
Human glial cells differentially express mRNA encoding for the NOP receptor and where present, this was translated into NOP receptor protein as determined using [leucyl-3H] N/OFQ binding (Table 1). In functional assays, N/OFQ significantly inhibited wound healing/cell migration in cells expressing NOP receptors (Table 1).

Overall, these findings suggest that NOP may have a role to play in astrocyte and oligodendrocyte function.

This work is sponsored by the Higher Committee for Education Development in Iraq HCED/Office of the Prime Minister/Iraq.

References:
De Vries, G.H. and Boullerne, A.I. (2010). Glial cell lines: an overview. Neurochemical research, 35, 1978-2000.
Giaume, C., et al (2007). Glia: the fulcrum of brain diseases. Cell death and differentiation, 14, 1324-1335.
Lambert, D.G. (2008). The nociceptin/orphanin FQ receptor: a target with broad therapeutic potential. Nat Rev Drug Discov, 7, 694-710.

Cell type	NOP Receptor		% of wound healing	
	mRNA (ΔC_T)	fmol ([^{3}H] N/OFQ)/mg protein	Control	N/OFQ
1321N1	12.3±1.1	99±34	41.6±2.1	32.4±1.4*
MO3.13	5.5±1.7	50±14	32.1±1.6	24.1±1.5*
HOG	12.4±0.1	116±31	50.8±3.9	36.2±4.2*
EOC-20	Undetected	Not tested	Not tested	

Table 1: Expression of NOP mRNA by PCR (ΔC_T; cycle threshold (C_T) NOP– housekeeper, low value is high expression, n=5), NOP receptor expression in saturation binding assays using [^{3}H] N/OFQ (n=4) and inhibition of wound healing (at 30h, n=5). All data are mean ±SEM. P≤0.05 compared to control (t-test).*

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Poster number: P-T080
Theme: Neuronal, glial & cellular mechanisms

Protocatechuic acid ethyl ester (EDHB) effects on cell viability and synaptic signalling in rat hippocampal and organotypic slices

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In order to maintain a healthy brain a constant supply of oxygenated blood is required. During hypoxia multiple signalling pathways are activated within neurons including the stabilisation of hypoxia-inducible factors. The activity of these proteins is regulated by O2, Fe2+, 2-OG & ascorbate-dependant hydroxylases which contain prolyl-4-hydroxylase domains (PHDs). Very little research has been carried out on the action of PHD inhibitors in the CNS and especially on synaptic transmission and plasticity. In this study we have investigated the acute effects of the PHD inhibitor and hypoxia mimetic, protocatechuic acid ethyl ester (EDHB) on cell viability and synaptic plasticity in isolated rat (Wistar) hippocampus and organotypic cell culture. Cell viability was assessed using propidium iodide in organotypic cultures. Excitatory post-synaptic potentials were elicited by stimulation of the medial perforant (mDG) or Schaffer collateral pathway. Long-term potentiation (LTP) was induced by high frequency stimulation. 2 or 24 h treatment with EDHB (100 µM) had no significant effect on hippocampal cell viability when compared to controls. Cultures treated with 24h hypoxia, 8h OGD or 24h excitotoxicity (Glutamic acid) showed a significantly higher percentage of cell death compared to control and EDHB treated cultures. EDHB (100µM) gave rise to an acute, inhibitory effect on synaptic transmission which was seen in the mDG but not in the CA1. There were no changes in the ratio of paired responses (50ms interval) after EDHB application suggesting a post-synaptic mechanism of action. EDHB at higher concentrations (100µM), was found to inhibit LTP in both the mDG and CA1 regions. Application of exogenous iron (100µM) and the HIF-inhibitor digoxin (100nM) did not reverse EDHBs inhibitory effect on baseline transmission or LTP, suggesting a HIF-independent mechanism of action. These results highlight a novel modulatory role for the PHD inhibitor EDHB in hippocampal synaptic transmission and plasticity. The effects are unlikely to be mediated pre-synaptically as is observed in hypoxia, where O2 levels are decreased in brain tissue and adenosine receptors are activated. A novel post-synaptic mechanism of action may be involved possibly involving NMDA & GABA receptor activation.

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Poster number: P-T081
Theme: Neuronal, glial & cellular mechanisms

Effects of auxiliary subunit GSG1L on the functional properties of native and recombinant AMPA receptors

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AMPA-type glutamate receptors (AMPARs) mediate fast excitatory neurotransmission in the mammalian brain and play key roles in synaptic plasticity and synapse development. Furthermore, AMPAR dysregulation contributes to neuron damage in a number of neurological conditions. The AMPAR pore-forming subunits, GluA1-4, are differentially expressed between cell types and ages, providing considerable functional diversity. This diversity is further increased by a variety of auxiliary transmembrane proteins that coassemble with AMPAR subunits to form macromolecular complexes. These associated proteins regulate receptor trafficking, gating and pharmacology. Proteomic studies identified the tetraspanin GSG1L as an AMPAR-interacting protein. Structurally similar to the transmembrane AMPA receptor regulatory proteins (TARPs), GSG1L has been validated as a bona fide AMPAR auxiliary protein capable of modulating channel gating and cell surface expression. To investigate further the possible roles of GSG1L we have explored its functional effects in various types of AMPAR assembly. Specifically, we recorded currents activated by fast application of glutamate onto outside-out membrane patches from cells expressing distinct combinations of AMPAR pore-forming subunits and auxiliary proteins. Furthermore, we investigated the importance of the C-tail of GSG1L in modulating AMPAR properties, by examining the effects of C-tail deletion (GSG1L-ΔCt). To determine the functional effects of GSG1L on native AMPAR complexes we manipulated its expression in different types of neuron and analyzed their synaptic currents. Using this approach we found that GSG1L exhibits subtype-specific effects on AMPARs. Our data show that while GSG1L slows desensitization in all AMPAR subtypes tested, the slowing of recovery from desensitization is limited to homomeric calcium-permeable AMPARs. Moreover, GSG1L mediates this recovery phenotype via an unusual carboxyl domain- and polyamine-dependent mechanism.
Supported by the Wellcome Trust (086185/Z/08/Z to SGC-C and MF) and the MRC (MR/J002976/1 to SGC-C and MF, MR/J012998/1 to MF and SGC-C).

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Poster number: P-T082
Theme: Neuronal, glial & cellular mechanisms

Chronic exposure to chemotherapy impairs neurogenesis in Sox1-GFP trangenic mice

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Purpose: Recent patients studies have demonstrated an association between chemotherapy treatment and cognitive impairment. We have previously shown that 5-fluorouracil, a chemotherapy agent widely used for breast, prostate and bowel cancer, induces cognitive impairments and a reduction in hippocampal neurogenesis in a rodent model. In the present study we quantified the impact of chronic 5-FU treatment on cell proliferation (Ki67), differentiation (DCX) and stem cell subpopulations (GFP and GFAP) in the subgranular zone (SGZ) of SOX1-GFP transgenic mice. > 90% of SOX1+ cells are neural stem cells and are restricted to SGZ. In SOX1-GFP mice it is possible to distinguish between early radial and later horizontal orientated SOX1+ cells and to distinguish quiescent (GFAP+) and activated (GFAP-) SOX1+ cells.

Methods: Male SOX1-GFP mice were injected with 5-FU or saline twice a day, every second day for two weeks. Animals were killed 24h after the last injection and their brains were processed for immunohistochemistry. Confocal images were acquired and analysed using ImageJ software.

Results: Two weeks of 5FU treatment caused a significant reduction in the number of proliferating (Ki67+) cells but did not affect the number of differentiating (DCX+) cells. A different picture emerged from the examination of neural stem cell subpopulations where chemotherapy reduced the number of quiescent (SOX1+/GFAP+) and activated (SOX1+/GFAP-), radial neural stem cells but had no effect on the numbers of horizontally orientated SOX1+ cells present in later stages of neurogenesis.

Conclusions: Results presented here demonstrate that chronic 5FU has a severe effect on hippocampal neurogenesis by inducing depletion of early neural stem cells, an effect which explains the prolonged reduction in hippocampal neurogenesis and cognitive impairments found in patients and animal models. Further experiments will look at the potential protective effect of fluoxetine and indomethacin on neurogenesis.

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Poster number: P-T083
Theme: Neuronal, glial & cellular mechanisms

The role of protrudin on neuronal morphology and axonal transport in primary cortical neurons

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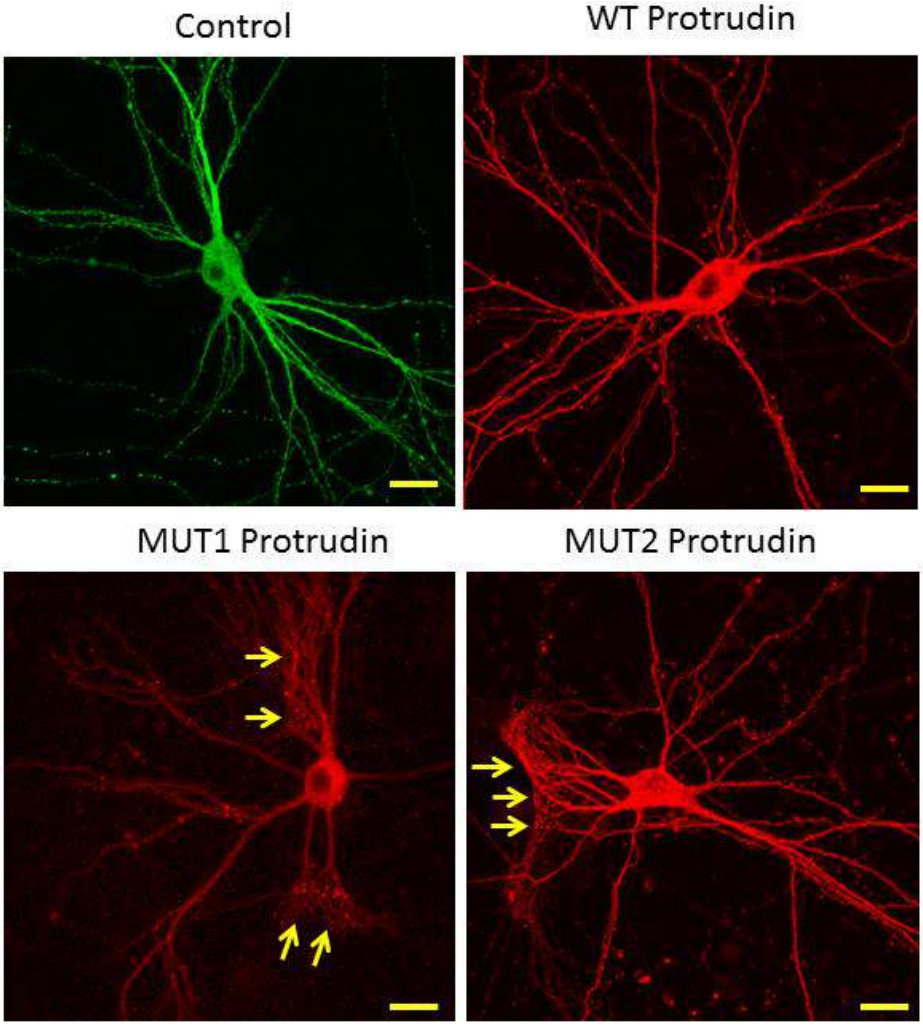
During development, neurons are fully equipped with growth machinery to extend long axons, reach their target cells and form functional connections. Once these connections have been established, the elongation capacity of neurons declines dramatically. One reason why adult CNS axons have poor regenerative capabilities might be that a developmental change occurs where essential growth molecules such as integrins become excluded from axons. Our laboratory is particularly interested in elucidating the transport mechanisms and the machinery needed to transport integrins and other growth-associated molecules to the tip of injured axons in order to design strategies to promote regeneration. Protrudin, a newly discovered member of the ZFYVE family of zinc-binding proteins, is a peripheral membrane protein involved in neurite outgrowth and directional membrane trafficking in HeLa and PC12 cells (Shirane et al., 2006). Interestingly, phospho-protrudin binds to a small GTPase, Rab11 which is involved in selective trafficking of growth-associated cargo along axons and this interaction is necessary for neurite outgrowth. Here, we hypothesise that promoting the association of protrudin with Rab11 (by creating phosphomimetic forms of protrudin) will result in an increased anterograde axonal transport of growth molecules which will potentially lead to increasing the regenerative capacity of mature cortical neurons. Firstly, the localisation of endogenous protrudin in cortical neurons was studied with maturation – as neurons mature, protrudin seems to be downregulated in axons compared to dendrites, which is a phenomenon observed with integrins and Rab11 distribution as well. Interestingly, protrudin seems to be localised to the proximal part of the axon in mature cortical neurons. Furthermore, overexpression of the phosphomimetic forms of protrudin resulted in morphological changes in dendrites by creating a complex dendritic branching in the form of “hairy” structures. Currently, the effects of phospho-protrudin overexpression on Rab11-dependant integrin transport and on the regenerative capacity of mature cortical neurons are being studied.

Shirane M., Nakayama K. (2006) Protrudin induces neurite formation by directional membrane trafficking. Science, 314: 818-821.



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Poster number: P-T084
Theme: Novel treatments & translational neuroscience

miRNA Biomarkers of Prodromal and Dementia stages of Alzheimer's disease in peripheral bio-fluids

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With the development of new therapeutics for Alzheimer's Disease (AD) , practical diagnostic methods for early stages have increased importance. AD manifests itself as a amnesic syndrome and diagnosed by specific deficits in cognitive function but recent findings revealed that the pathogenesis of AD precedes the onset of these symptoms by up to 30 years with a gradual build-up of Amyloid Beta and Neurofibrillary tangles progressing going through 3 stages of the disease; the symptomless Preclinical stage, the Prodromal stage, manifesting as a Mild Cognitive impairment (MCI) which gradually progresses to dementia and full AD. The build-up of toxic misfolded proteins A-Beta/Phos-tau and their downstream effects is thought to be too advanced and irreversible at the time of conventional diagnosis and thus the discovery of new biomarkers to help diagnose earlier prodromal stages of Alzheimer's disease is essential for the development of effective AD treatments. MicroRNAs are prime candidates for detecting early stages of AD with a distinct dysregulation in neuronal diseases, stable strucutre in extracellular environment and being able to readily pass the blood brain barrier. We focused on identifying miRNA biomarkers within minimally invasive biofluids, screening peripheral blood samples and Tear Fluid. Blood and tear fluid sample were collected from patients (n=30) clinically diagnosed with MCI and AD. Blood plasma and tear fluid microRNA were isolated and pooled for Open-array analysis followed by individual qPCR validations of miRNA candidates selected from OpenArray. Several miRNA biomarker candidates were identified in AD and MCI, validated within individual qPCRs, both novel and previously identified biomarkers within blood plasma as well as Tear Fluid. These results we potentially have identified biomarkers for AD and precursor stages which can be detected from a blood sample, d, tear fluid results are evidence that tear fluid is novel source of miRNA biomarkers for neurodegenerative diseases.

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Poster number: P-T085
Theme: Novel treatments & translational neuroscience

Investigating a Fragment of the Leptin C-D loop: Neuroprotective and Behavioural Effects

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Introduction
Leptin regulates satiety and energy homeostasis via the hypothalamus but receptors are expressed throughout the brain including the hippocampus, indicating potential additional roles for leptin within the CNS. Leptin's beneficial effects on memory are well established and it has been shown to increase amyloid-β and tau pathology clearance. Although this indicates leptin may be beneficial as a therapeutic in Alzheimer's disease, leptin administration can induce a number of side effects. Additionally, it is expensive to manufacture and difficult to administer. As such we aim to identify a bioactive fragment of leptin which will produce the beneficial effects within the CNS with reduced peripheral side effects.

Materials and Methods
Differentiated SH-SY5Y cells demonstrating a neuronal phenotype were used to identify the effectiveness of leptin or leptin116-130 treatment in protecting against cell death, determined via LDH and crystal fast violet assays. Protein extracted from these cultures was used for ELISA to determine downstream signalling. Finally, C57 mice were used in an object-place-context memory task and treated with full-length leptin, leptin116-130 or saline to identify effects on episodic memory.

Results
Leptin and leptin116-130 were able to protect from cell death induced by copper chloride or amyloid-β. Furthermore, leptin116-130 activates both STAT3 and Akt pathways, confirming its status as a leptin mimetic. The OPC memory test showed mice treated with either leptin or leptin116-130 had significantly enhanced memory compared to saline-treated controls.

Conclusions
Leptin116-130 is sufficient to replicate known survival-promoting effects of leptin in neuronal cell cultures and activates key leptin-linked signalling cascades. Further it can enhance the performance in an OPC task, suggesting it is a valid therapeutic target in fight against AD.

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Poster number: P-T086
Theme: Novel treatments & translational neuroscience

Targeting the Tetrahydrobiopterin Pathway for the Development of Novel Analgesic Compounds

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A clinical need for novel approaches in the treatment of chronic neuropathic pain (NP) is essential to address an emerging issue in modern pain treatment, with a severe lack of effective pharmacological interventions comprising of antidepressants, opioids and anticonvulsants. Efforts to elucidate the de novo pathway in tetrahydrobiopterin (BH4) synthesis have shown promising analgesic drug targets in guanosine triphosphate cyclohydrolase 1 (GCH1), and sepiapterin reductase (SPR). The de novo enzymatic pathway is of interest in NP research as it is significantly increased in response to damaged or hyperactive peripheral nociceptors, inducing the synthesis of BH4 through GCH1 upregulation, the rate-limiting step in BH4 synthesis from guanosine triphosphate (GTP). Artificial stimulation of the BH4 pathway, highly active in a variety of immune cell lines by inflammatory cytokines such as interferon gamma (IFN-γ) in vitro cause a huge upregulation in GCH1 expression levels. This has been used as a pharmacological model for the identification of novel compounds for the treatment of NP, that inhibit the BH4 de novo synthesis pathway through GCH1 or SPR antagonism.
A small molecule library of 32 novel potential GCH1 inhibitors have been synthesised at the University of Huddersfield. Compounds were tested in comparison to the GCH1 inhibitor 2,4-Diamino-6-hydroxypyrimidine (DAHP) for their inhibitory properties of the GCH1 enzyme in a Neopterin ELISA assay. Neopterin formation in cell lysates of IFN-γ plus drug treated THP-1 monocytes was determined and used as a measure of GCH1 activity.
Addition of 1mM DAHP significantly reduced stimulated THP-1 neopterin production from 64.6 (±10.8) nMol/L to 4.5 (±4.2) nMol/L, close to basal levels of non-stimulated THP-1 cells of 2.74 (±2.18) nMol/L (n=9 for all). A number of compounds from the library caused significant reductions ($p \leq 0.05$, n=6) in neopterin concentration of IFN-γ stimulated THP-1 at 10 µM concentrations.
These results show potential in a select number of compounds from the library as inhibitors of GCH1 enzyme activity in the BH4 pathway. Further pharmacological analysis will be performed to build up compound profiles and assess their suitability as potential novel analgesics in the treatment of NP.

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Poster number: P-T087
Theme: Novel treatments & translational neuroscience

Impairment of cocaine-mediated behavioural responses by clinically relevant Ras-ERK inhibitors

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Ras-ERK pathway plays a central role in drug addiction. However, to date, no inhibitors of this cascade have been tested in experimental models of addiction. In order to develop new pharmacological tools acting on this signalling cascade two novel cell-penetrating peptides (CPPs), RB1 and RB3, were designed upon the docking domain of the phosphatase MKP-3 (RB1) and the Ras interacting domain of Ras-GRF1 (RB3), respectively.

RB1 and RB3 CPPs are able to inhibit the ERK pathway in a dose-dependent manner, within the low micromolar range, in an ex-vivo model of adult striatal slices. Importantly, in vivo, these two peptides not only prevent ERK signalling activation in response to cocaine but also block cocaine-induced place preference upon a single systemic administration.

In addition, we demonstrated that PD325901, a potent MEK inhibitor already in clinical trials for cancer, is able to penetrate the brain and efficiently inhibit Ras-ERK pathway within the nanomolar range. Furthermore, a single in vivo administration of PD325901 persistently blocks cocaine-induced place preference and significantly accelerates the extinction of cue-induced responding following cocaine self-administration.

Altogether, our results suggest that these drugs may represent a new valuable therapeutic approach to treat brain disorders characterised by an abnormal hyperactivation of Ras-ERK signalling, such as cocaine addiction.

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Poster number: P-T088
Theme: Novel treatments & translational neuroscience

Cognitive impairments in the rodent depression model of chronic mild stress assessed by touchscreen operant learning paradigms

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Currently depressed (60-70%) and remitted patients (30-50%) suffer from cognitive impairments in functional domains of memory, executive function and attention. Cognitive impairments are often neglected when confronted with the burdensome core symptoms of depression: depressed mood, anhedonia and lack of energy. To date, procognitive treatment in depression is inadequate. Thus, a valid animal model is crucial for assessment of procognitive effects of novel and conventional antidepressants. Further, focus should be on translational tasks when addressing such a complex domain as human cognition. We investigated these impairments by using the validated chronic mild stress (CMS) paradigm for provoking a depressive-like phenotype in rodents. The CMS model includes good predictive, construct and face validity and elicits the core symptom anhedonia. We assessed cognitive performance of these rodents with a highly translational test apparatus –the touchscreen operant platform. It was developed based on the Cambridge Neuropsychological Test Automated Battery (CANTAB), a cognitive assessment tool for humans.

To evaluate learning and retention, we applied the rodent-version of the paired-associates learning (PAL) touchscreen task. It involves object-location association learning and we added a retention phase after a 10 day hiatus. Two phenotypes were induced by CMS exposure and included in the study: a stress susceptible (n = 10) and resilient (n = 9) group defined by their hedonic state.

We found a trend for the mean number of trials needed to acquire the PAL task ($F(2, 26) = 3.30$, $p = .053$). Non-stressed controls (n = 10, M = 1307, SD = 556) needed fewer trials than stress susceptible rats (M = 1824, SD = 485, $p = .021$). Stress resilient rats did not differ significantly (M = 1428, SD = 324, Fisher's LSD).

We conclude that this finding suggests impaired cognition in stress susceptible, depressive-like rats as they need more training to learn the task. This was not found in resilient rats, suggesting that the depressive-like state, rather than the general exposure to stress, causes this impairment. Hence, we believe that further studies and data analysis will confirm this trend allowing highly translational testing in a well validated rodent model of depression.

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Poster number: P-T089
Theme: Novel treatments & translational neuroscience

Thalamic atrophy in patients with newly-diagnosed focal epilepsy

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Background
Prospective imaging studies of newly diagnosed epilepsy (NDE) may yield important information about the natural course of epilepsy and its treatment. However, patients have only rarely been studied from the time of diagnosis, despite this being a key point in time to understand the underlying biology of epilepsy and to identify potential interventions and biomarkers for seizure and cognitive outcomes. In the present study, we performed a quantitative MRI study of subcortical structures known to play a role in seizure modulation and propagation regardless of the epileptogenic focus in patients with focal NDE.

Methods

We studied 101 patients with focal NDE and 40 neurologically healthy controls. All participants received an MRI protocol that included high in-plane resolution T1-coronal images (0.4 mm x 0.4 mm x 3 mm) on a 3 T MRI system at the Walton Centre NHS Foundation Trust, Liverpool. MRI scans were obtained within one year of epilepsy diagnosis. Focal epilepsy was diagnosed by expert neurologists at the Walton Centre. Quantitative MRI measurements of the left and right thalamus, putamen and caudate nucleus was performed for all participants using stereology in conjunction with point counting. Volumetric comparisons were made between patients and controls.

Results
Relative to controls, the left (U=1294, p=0.001) and right (U=1488, p=0.015) thalamus were significantly smaller in patients (Figure 1). Eleven patients (11%) had thalamic volumes two standard deviations lower than the mean of control volumes, eight of these patients displayed this atrophy bilaterally (8%). There were no statistically significant differences between patients and controls in volume of the left (U=1936, p=0.701) or right (U=1888, p=0.546) putamen and left (U=1806, p=0.328) or right (U=1846, p=0.426) caudate nucleus.

Conclusion
Patients with focal epilepsy are neuroanatomically compromised at the point of diagnosis. To our knowledge, this work is the first to reveal thalamic atrophy in NDE, and suggests that previously reported thalamic abnormalities in patients with longstanding focal epilepsy are not necessarily a result of the chronicity of the disorder, and may potentially contribute to predisposing patients to seizures and cognitive dysfunction.

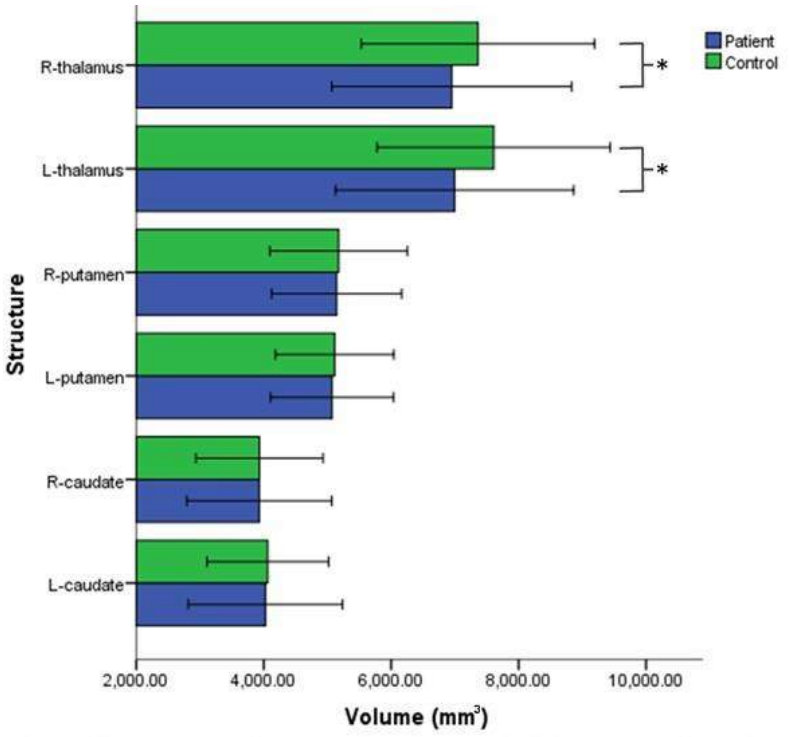

Figure 1. Means and standard deviations of structural volume measurements. The left and right thalamus were found to be significantly reduced in volume in patients with newly-diagnosed focal epilepsy compared to healthy controls. *Notes *p<0.05*

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Poster number: P-T090
Theme: Novel treatments & translational neuroscience

Cannabidiol dampens the expression of auditory fear memory without affecting its extinction in rats

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Anxiety-related disorders like phobias and post-traumatic stress are highly prevalent and their treatment using psychological therapies or medications can be ineffective. A promising area of study involves using drugs to enhance exposure therapy to treat these disorders. Cannabidiol, the major non-psychotropic phytocannabinoid of Cannabis sativa, shows broad therapeutic potential for treating anxiety. Evidence from translationally relevant animal models indicates that cannabidiol reduces innate fear and learned fear expression induced by contextual cues while also enhancing contextual fear extinction, which is the psychological process by which exposure therapy reduces fear memory expression. However, the effects of cannabidiol on learned fear expression and extinction related to discrete cues is poorly understood.

Here we investigated the effects of cannabidiol on learned fear expression and its extinction using an auditory fear conditioning paradigm in rats. On Day 0, rats were habituated to contexts A and B. On Day 1, rats underwent tone habituation followed by auditory fear conditioning (tone-shock pairings) in context A. On Day 2, rats were treated with cannabidiol (5, 10, or 20 mg/kg, i.p.) or vehicle before undergoing extinction (tones presented alone) in context B. On Day 3, rats underwent extinction recall testing (tones presented alone) drug-free in context B. Freezing during tone presentations was quantified as the measure of conditioned fear.

We found that 20 mg/kg of cannabidiol significantly decreased freezing during early extinction, compared to vehicle, but there were no drug effects on freezing later on during extinction. Moreover, there were no differences in freezing during extinction recall between the groups the following day. These results indicate that 20 mg/kg of cannabidiol dampened auditory fear expression at the start of extinction without affecting extinction learning or memory consolidation. Taken together, our results showing dampened learned fear expression combined with spared extinction suggest that cannabidiol is an interesting therapeutic candidate for fear management when used as a pharmacological adjunct to reduce anxiety during exposure therapy without interfering with its benefits or having adverse side effects.

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Poster number: P-T091
Theme: Novel treatments & translational neuroscience

In vitro modulation of rodent prefrontal gamma oscillations by a novel Kv3 channel modulator following sub-chronic PCP treatment

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Cognitive dysfunction is a hallmark symptom of schizophrenia. Studies in patients with schizophrenia and preclinical animal models have shown a disruption of synchronized high-frequency network activity and a dysfunction of parvalbumin-positive (PV+) GABAergic interneurons, both of which are critical for cognitive processing. Inhibitory fast-spiking PV+ interneurons orchestrate synchronized activity by firing at gamma (30-80 Hz) frequencies and entraining large populations of cortical pyramidal cells. The fast spiking properties and high temporal fidelity of PV+ interneurons are endowed by the selective expression of Kv3.1 potassium channels on these cells. Thus, targeting Kv3 channels, and enhancing the activity of PV+ interneurons, has potential as a pharmacological treatment for schizophrenia.

Using the sub-chronic phencyclidine (PCP) rodent model, we examined the effects of a range of concentrations of a novel Kv3 modulator (1, 3, 10, 20 uM AUT00206) in vitro. Prior to brain slice in vitro studies, animals were behaviourally tested (novel object recognition task) to confirm cognitive deficits in PCP treated rats versus vehicle treated rats. Kainate/carbachol induced gamma oscillations were recorded from prelimbic (PrL) and infralimbic (IL) regions of prefrontal cortical slices obtained from both groups of animals.

Results demonstrate that higher concentrations of AUT00206 (10 and 20 uM) significantly increased the area power of gamma oscillations in the PrL region in slices from PCP treated rats (10 uM: 250 ± 59 uV^2 v. 301.7 ± 88 uV^2, 21.4 ± 8.9%, p = 0.02, n = 10; 20 uM: 148.6 ± 71 uV^2 v. 157.6 ± 59 uV^2, 27.2 ± 10.2%, p = 0.037, n = 10). Slices from vehicle treated animals showed a significant reduction in gamma area power at 20 uM AUT00206 (209.1 ± 99 uV^2 v. 131.7 ± 57 uV^2, -29.5 ± 7.3%, p = 0.016, n = 8). A similar effect of AUT00206 was observed in the IL region, however only the 10 uM concentration produced a significant increase of gamma in the PCP group (305.7 ± 120 uV^2 v. 380 ± 180 uV^2, 14.6 ± 6.6%, p = 0.046, n = 14).

Our results suggest that modulation of Kv3 channels by AUT00206 may have the potential to correct aberrant neuronal oscillations in patients suffering from schizophrenia by augmenting gamma frequency oscillations.

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Poster number: P-T092
Theme: Novel treatments & translational neuroscience

Systemic administration of a Connexin43 mimetic peptide is neuroprotective and improves functional recovery after spinal cord injury in rats

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Connexin43, a gap junction protein, is up-regulated following spinal cord injury (SCI) and contributes to secondary lesion spread. Peptide5, a mimetic peptide derived from the second extracellular loop of the Connexin43 protein, has been previously shown to reduce tissue damage and improve functional outcomes when delivered directly to SCI lesion site intrathecally. We have now investigated whether systemic delivery results in similar outcomes. Rats were subject to a 10g, 6.25mm weight drop injury at the vertebral level T10 using a MASCIS impactor. Peptide5 or control scrambled peptide was administrated intraperitoneally post-injury. Rats were then assessed for locomotor recovery and pain hypersensitivity and euthanised at 8 hours (n=8), 24 hours (n=32), 2 weeks (n=32) or 6 weeks (n=32) post-injury. Treatment with Peptide5 led to significant improvements in hindlimb function as assessed using the Basso-Beattie-Bresnahan scale and the error ladder test between 3 and 6 weeks following injury. In addition, there were reductions in at-level mechanical allodynia post-injury. Peptide5 caused a significant reduction in lesion size at all post-injury time points. Immunohistochemistry showed that Peptide5 treatment reduced Connexin43 protein and increased the phosphorylated Connexin43 protein levels at 8 hours after injury compared to the control treatment group. At 2 and 6 weeks following SCI, immunohistochemistry of tissue sections demonstrated reductions in astrocytic (GFAP) and activated macrophage and microglial (Iba1/ED1) responses, as well as an increase in neuronal survival (NeuN) at the dorsal and midline levels, compared to the controls. These results suggest that systemic administration of Peptide5 modulates the pathological opening of Connexin43 hemichannels at the lesion site to ameliorate the secondary damage resulting from SCI and has a significant effect on improving functional outcomes. This preclinical research has successfully demonstrated the therapeutic efficacy of Peptide5 in an animal model, and provides a strong basis for further translational studies.

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Poster number: P-T093
Theme: Neurodegenerative disorders & ageing

The Childhood Neurodegenerative Disease Gene, CLN7 Regulates Synaptic Development in Drosophila from the postsynaptic side

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Early onset neural pathology is characteristic of many inherited lysosomal storage disorders suggesting lysosomal function is essential for the development of the nervous system. However, exactly why lysosomal function is required for neural health is poorly understood. Mutations in the CLN7 gene which encodes a lysosomal transmembrane protein results in Neuronal Ceroid Lipofuscinoses (NCL), an inherited lysosomal storage disorder with late infant-onset neurodegeneration. The biology underpinning the disease is not known but the early onset of pathology suggests roles for CLN7 in neural development. We have taken advantage of the genetic tractability of Drosophila to examine CLN7 function in the development of the larval neuromuscular junction, a well-established model for studying synaptic development and function. We have generated mutations in CLN7 and used gene editing tools to create knock-in reporters to study its function and to identify where it is expressed in the developing fly. We find CLN7 mutants exhibit reduced synapse size, likely due to hyperactivation of mTORC signalling causing downregulation of autophagy.

These developmental changes impact on the electrical properties of the synapses and on movement of the animal. Surprisingly, our knock-in reporters reveal CLN7 is largely absent from neurons but strongly expressed in subsets of glia and in the body-wall muscles which form the post-synaptic side of the neuromuscular junction. Knockdown of CLN7 function specifically in the muscle is sufficient to replicate the neurodevelopmental phenotypes of the mutant, suggesting CLN7 may regulate synaptic development via BMP-mediated retrograde signalling.

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Poster number: P-T094
Theme: Neurodegenerative disorders & ageing

Investigating cellular stress related responses in a mouse model of fronto-temporal dementia

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Neurodegenerative diseases are associated with the accumulation of misfolded proteins. In response to these insults cells generate different responses, including activation of the immediate early genes. However, it is still unclear if these transcriptional activations are protective or if they may exacerbate neurodegeneration.

In Alzheimer's disease and other dementias aggregates of microtubule binding protein tau are observed. Malfunctioning of tau is one of the main cellular insults in these diseases.

Mutations in tau gene, such as P301L, are responsible for fronto-temporal dementia (FTD) and it is a well-characterized and often used model to study tau pathology.

We are using the transgenic rTg(tauP301L)4510 mouse model of FTD, which overexpresses this mutant tau. Using quantitative PCR and Western blot, we compared the expression of unfolded protein response (UPR) and other stress-related genes in the P301L mice and control mice. Cortical tissue from mice at 6 month of age and 12 month have been used to investigate the levels of stress markers at times points that initiate and progress neuropathology. We are mainly interested in the UPR components (ATF4, XBP1, BiP), activity-induced responses (Arc, c-Fos, c-Jun) and changes related to general insults (ATF3, GADD45) that are commonly found in other disease models.

We have detected no change in the level of expression of UPR components in mice at 6 month of age. In contrast we have observed changes in the expression of some immediate early genes and GADD45. We are repeating this analysis at the later time point to initiate an investigation of the time course of these changes. In particularly we want to probe if the UPR becomes induced by the progressed tau dysfunction.

After identification of the stress-related changes induced in rTg4510 model, we will modulate signalling mediated by stress responses to define if they are neuroprotective or cause neurodegeneration. Describing these intracellular pathways could help to understand the pathology and develop potential treatments for tauopathies.

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Poster number: P-T095
Theme: Neurodegenerative disorders & ageing

Neural mechanisms of spatial and temporal orienting in aging

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Recent research has tried to delineate in how far the mechanisms of spatial and temporal orienting can be preserved with aging. Specifically, it has been claimed that older adults cannot use temporal information to improve performance, which was supported by neural evidence suggesting a lack of pre-target temporal orienting (Zanto 2011). In addition, while older adults were shown to

exhibit most of the evoked markers of spatial orienting established in younger adults, cue-induced oscillatory lateralisation could not be found (Hong 2015).
We developed a multimodal attention study, where both spatial and temporal information were manipulated. Specifically, we combined behavioural testing with electroencephalographic recording (EEG) and functional magnetic resonance imaging (fMRI) and tested 24 healthy elderly participants.

We show that participants could benefit behaviourally from both spatial and temporal information. EEG analysis yielded significant effects on previously established cue (CNV, ADAN, LDAP) and target (N1 and P3 amplitude; P3 latency shift) evoked and induced (alpha lateralisation) modulations of attention. These results could be supported by regional evidence from fMRI, differentiating task positive and resting state networks.

We suggest that healthy elderly participants can engage in preparatory spatial orienting and extend recent behavioural findings on spared temporal orienting with aging (Chauvin 2016) to the neural domain.

The study serves as a baseline for a second branch of research, where we apply the paradigm to age-matched stroke survivors, assessing whether neural and behavioural signatures of spatial and temporal orienting are affected by focal subcortical and cortical lesions.

Chauvin et al. (2016). Temporal orienting of attention can be preserved in normal aging. Psychology and Aging, 31(5), 442–455.
Hong et al. (2015). Normal aging selectively diminishes alpha lateralization in visual spatial attention. NeuroImage, 106, 353–363.
Zanto et al. (2011). Age-related changes in orienting attention in time. The Journal of Neuroscience?: The Official Journal of the Society for Neuroscience, 31(35), 12461–12470.

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Poster number: P-T096
Theme: Neurodegenerative disorders & ageing

Spinal cord pathology in multiple forms of Batten Disease or Neuronal Ceroid Lipofuscinosis (NCLs)

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The NCLs are a group of rare lysosomal storage disorders, which mainly occur in children and result in severe neurodegeneration and premature death. There are currently no treatments available for any form of NCL and for any therapy to be successful it is imperative to target them to all affected areas. This is especially important for the transmembrane-protein deficient forms of NCL, which cannot be treated via the principle of cross-correction. We have recently found that in CLN1 disease the spinal cord is profoundly affected at a surprisingly early disease stage. We are now extending this analysis of possible spinal pathology to other forms of NCL, including CLN3 and CLN7 disease.

We have undertaken an unbiased stereological assessment of neuron loss, astrocytosis and microglial activation in both Cln7KO and Cln3KI mouse models at different stages of disease progression. Analysing sections of cervical, thoracic and lumbar spinal cord sections has revealed a significant loss of neurons throughout all levels of the spinal cord in Cln7KO mice, as well as a significant loss of white and grey matter volumes. There also was a profound amount of astrocytosis and microglial activation throughout the whole Cln7KO spinal cord, as well as a loss of interneuron populations. Preliminary data from Cln3KI mice reveal less pronounced glial activation, and neuronal cell counts are underway.

Based on these findings, the nature and extent of spinal neuropathology appears to differ between forms of NCL. Defining the precise onset and progression of these changes and their relationship to events in the brain and peripheral nervous system will be important for devising and delivering more efficient therapeutic approaches in these profoundly disabling disorders.

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Poster number: P-T097
Theme: Neurodegenerative disorders & ageing

Banking on Brains: The London Neurodegenerative Diseases Brain Bank as a resource for the neuroscience community

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Human post-mortem brain tissue remains one of the most important resources for neuroscience research and its collection and provision is essential if we are to develop new strategies and treatments for neurodegenerative disease. The scientific value of the tissue is greatly increased when accompanied by in depth clinical and neuropathological assessment.

The London Neurodegenerative Diseases Brain Bank has collected over 2000 cases since its establishment in 1989 – comprising formalin fixed and frozen brain and spinal cord samples and frozen CSF. We are constantly updating our procedures to ensure tissue is of the best quality for use in current research techniques, striving to reduce post-mortem delay, limit pH change and maintain DNA/RNA integrity.

We have collections of a wide variety of diseases comprising largely of neurodegenerative diseases, including Alzheimer's disease, Dementia with Lewy Bodies, Motor Neurone Disease and Frontotemporal dementia. However, we also collect tissue from rarer diseases, such as psychosis, head injury and paediatric disorders. In order to provide comparative control tissue we also house a strong collection of healthy brain and spinal cord tissue. All donations undergo a comprehensive histological examination to provide detailed information on disease pathology.

The brain bank operates a transparent and open-door policy for provision of this tissue to researchers. Tissue requests are reviewed by a request committee and responded to in a timely fashion. In the last five years we have completed over 250 requests and have provided over 120,000 samples to national and international institutions.

We are a founding member of the 'Brains for Dementia Research' network – a cohort of over 3000 volunteers which combines longitudinal clinical assessments in life with subsequent brain donation. To maximise the availability and research potential of our tissue we are also part of the 'MRC UK Brain Bank' network which aims to encourage and facilitate both tissue donation and tissue accessibility for researchers.

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Poster number: P-T098
Theme: Neurodegenerative disorders & ageing

Individual differences in neural mechanisms of superior cognitive ageing: structure, function and cognition

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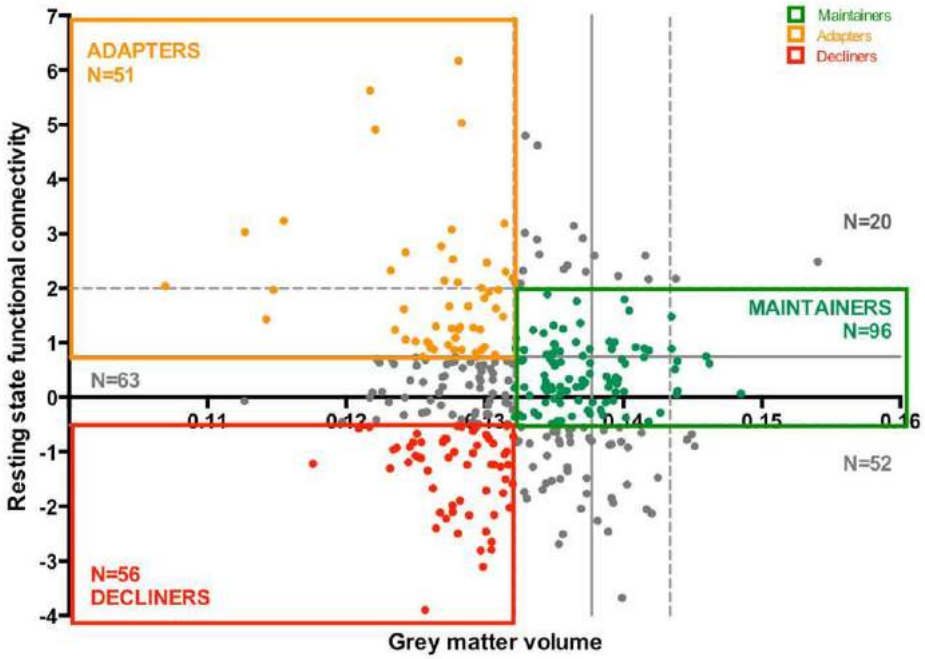
Whilst cognitive decline is common in old age, some older adults retain intact cognitive abilities, but the neural basis of this is unclear. We aimed to provide direct evidence for individual differences in neural mechanisms of superior cognitive ageing. Using literature-based brain metrics, we classified older adults as maintainers ('youthful' brain structure & function), adapters (increased function & reduced structure) or decliners (reduced structure & function) relative to younger adults, and predicted superior cross-sectional (CS) cognition and less longitudinal (L) cognitive decline in maintainers and adapters, vs decliners. White matter (WM) integrity was also compared between groups, as preserved WM may underlie higher brain function in adapters.

Method: 343 healthy older adults with L cognitive data from 1997-2013 completed an MRI scan (T1, DTI, fMRI) and further CS cognitive tests. For each subject, grey matter (GM) and resting state (RS) metrics were extracted from regions affected by age in a separate sample of old vs young adults, and classified relative to the mean and standard deviation GM and RS in young adults (Figure 1), resulting in 51 adapters, 96 maintainers and 56 decliners. Cognitive scores (CS & L) and fractional anisotropy (FA) maps of WM integrity were compared between groups.

Results: Contrary to prediction, CS cognition was higher in maintainers than both decliners and adapters. L decline was observed across all subjects, but rate of decline was not significantly different between groups. Decliners and adapters performed worse across time points on short term memory, vs maintainers. FA was significantly higher in adapters than decliners, and was positively correlated with RS.

Conclusion: We identified different brain patterns implicated in superior cognitive ageing, but found only maintainers showed superior cognition, suggesting higher RS activity in adapters is not compensatory. No group difference in L decline suggests adapters and decliners' poorer performance may reflect lifelong differences, rather than different trajectories of decline. Preserved WM may underlie higher RS in adapters, although whether this reflects a lifelong pattern or a change with age is unclear. Longitudinal imaging will expand on current findings.



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Poster number: P-T099
Theme: Neurodegenerative disorders & ageing

Activation of the pro-resolving receptor Fpr2 reverses inflammatory microglial activation

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Inflammation is a major contributor to many neurodegenerative disease (Heneka et al. 2015). Microglia, as the resident immune cells of the brain and spinal cord, provide the first line of immunological defence, but can become deleterious when chronically activated, triggering extensive neuronal damage (Cunningham, 2013). Dampening or even reversing this activation may provide neuronal protection against chronic inflammatory damage.
The aim of this study was to determine whether lipopolysaccharide (LPS)-induced inflammation could be abrogated through activation of the receptor Fpr2, known to play an important role in peripheral inflammatory resolution. Immortalised murine microglia (BV2 cell line) were stimulated with LPS (50ng/ml) for 1 hour prior to the treatment with one of two Fpr2 ligands, either Cpd43 or Quin-C1 (both 100nM), and production of nitric oxide (NO), tumour necrosis factor alpha (TNFα) and interleukin-10 (IL-10) were monitored after 24h and 48h.

Treatment with either Fpr2 ligand significantly suppressed LPS-induced production of NO or TNFα after both 24h and 48h exposure, moreover Fpr2 ligand treatment significantly enhanced production of IL-10 48h post-LPS treatment. As we have previously shown Fpr2 to be coupled to a number of intracellular signaling pathways (Cooray et al. 2013), we investigated potential signaling responses. Western blot analysis revealed no activation of ERK1/2, but identified a rapid and potent activation of p38 MAP kinase in BV2 microglia following stimulation with Fpr2 ligands.

Together, these data indicate the possibility of exploiting immunomodulatory strategies for the treatment of neurological diseases, and highlight in particular the important potential of resolution mechanisms as novel therapeutic targets in neuroinflammation.

References
Cooray SN et al. (2013). Proc Natl Acad Sci U S A 110: 18232-7.
Cunningham C (2013). Glia 61: 71-90.
Heneka MT et al. (2015). Lancet Neurol 14: 388-405.

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Poster number: P-T100
Theme: Neurodegenerative disorders & ageing

Inhibition of IL-34 blocks CSF1R-dependent microglial proliferation in the prion model of chronic neurodegeneration

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Microglia are the main resident immune cells in the central nervous system. The expansion and activation of microglia is a hallmark of many neurodegenerative diseases including Alzheimer's disease or prion disease. Colony-stimulating factor 1 receptor (CSF1R) is involved in the control of the microglial proliferation and can be activated by two independent ligands, CSF1 and IL-34. These two ligands display differences in the signalling cascade suggesting a complementary role1. However, although CSF1 and IL-34 are expressed in many organs, IL-34 appears particularly expressed in the developing and adult brain, suggesting that maintenance of the populations of microglia is dependent on IL-34-CSF1R signaling2. Therefore, the aim of this project is the evaluation of novel IL-34 blocking strategies that can be used to modulate microglia proliferation in neurodegenerative diseases by using an in vivo model of neurodegeneration (prion disease; ME7).

Anti-IL-34 blocking antibodies were injected in ME7 mice 12 weeks post-induction of disease. Daily injection of 5-Bromo-2-Deoxyuridine (BrdU) for 1 week was performed, in order to follow proliferation of microglia. One week after IL-34 blockade, immunochemistry analysis of BrdU showed a significant decrease in microglia proliferation in prion mice treated with an anti-IL-34 antibody compared to prion mice treated with an isotype control or with an IL-34 antibody directed against the human protein. Other measures of target engagement were conducted in order to understand the dynamics of IL-34 blockade, including measures of downstream pathways or soluble mediators.

These results provide validation data to support the hypothesis the concept that control of the microglial response through IL-34 blockade could be a potential therapeutic approach in neurodegenerative diseases.

1. Wei S. et al., Functional overlap but differential expression of CSF-1 and IL-34 in their CSF-1 receptor-mediated regulation of myeloid cells. J Leukoc Biol. 2010, 88(3):495-505.
2. Wang Y. et al., IL-34 is a tissue-restricted ligand of CSF1R required for the development of Langerhans cells and microglia. Nat Immunol. 2012, 13(8):753-760.

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Poster number: P-T101
Theme: Neurodegenerative disorders & ageing

Transient activation of NLRP3-inflammasome in the MPTP mouse model of Parkinson`s disease: interaction with HMGB1-MAC-1

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Mounting evidence suggests the involvement of the immune system in neurodegenerative disorders including Parkinson`s disease (PD) (Benkler et al. 2012; Clin Rev All & Immun. 42:164). We recently reported increased levels of HMGB1 in PD patients as well as in the MPTP animal model of PD (Santoro et al. 2016; Nuerobiol Dis 91:59). In the present study we explored whether the release of HMGB1 in our mouse model of PD caused the activation of the NLRP3 (NOD-like Receptor Protein 3) positive inflammasome. NLRP3-inflammasome is a multiprotein complex, and part of the innate immune system that is activated in aseptic conditions such

as tissue damage or metabolic impairment. Its activation leads ultimately to both formation and release of the proinflammatory cytokine IL-1? (Frank et al. 2016; Brain, Beh & Immunity 55:215).
C57BL6J mice were injected with the sub-acute regimen (30 mg/kg/day for five consecutive days i.p., control animals were injected with equivalent volume of saline solution) of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Brain tissue was harvested 1-2 days post-injection. Tissue was then prepared for double immunofluorescent staining of three different cell types: dopaminergic neurons, astrocytes and microglia, performed on midbrain sections inclusive of substantia nigra, or for western blotting experiments conducted on protein lysate from ventral midbrain.

Our confocal microscopy analysis confirmed an increase in NLRP3 protein levels in the cytoplasm of microglia one day after MPTP injections. In parallel, heightened levels of the microglial MAC-1 protein were confirmed histologically at the level of the substantia nigra and by western blotting. This up-regulation of MAC-l, a surface receptor for HMGB1, may therefore constitute a critical link in the activation of cytoplasmic pathways leading to activation of the NLRP3-inflammasome in Parkinsonism.

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Poster number: P-T102
Theme: Neurodegenerative disorders & ageing

Dementia on a Chip: Investigating Tau Spread in Microfluidic Devices

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Alzheimer's disease is characterised by the presence of β-Amyloid plaques and neurofibrillary tangles. Despite the increased incidence of this disease due to an ageing population, the exact cause of the disease is still unknown and is of great interest to the scientific and medical communities. There is inherent difficulty in studying the disease in vivo as it does not naturally occur in other species and working with animal models can be too complex to investigate cell biology and intracellular mechanisms. Therefore, we have used human induced pluripotent stem cell (HiPSC) derived cortical neurons cultured in microfluidic devices to investigate the mechanisms underlying the disease.

The microfluidic system used creates an in vitro model relevant to the spread of tau isoforms associated with Alzheimer's disease. The compartmentalised system involves a series of cell culture chambers connected via an array of microfluidic channels. This system allows two or more neuronal networks to form functional connections with adjacent networks whilst maintaining environmental isolation from each other.

We cultured HiPSC-derived neurons in microfluidic systems for 3-10 weeks prior to functional testing. Cells were derived from both control patients and those with 10+16 MAPT mutation that can lead to the formation of tau aggregates associated with frontotemporal dementia. Cells were cultured both in isolation and co-cultured with astrocytes to determine whether synaptic maturity was accelerated in these co-cultures.

Calcium imaging was used to demonstrate functional connectivity between networks in the microfluidic devices, where a primary network was chemically stimulated in isolation and the adjacent, secondary network exhibited a synchronous calcium response. To investigate tau spread, tau fibrils are seeded on one network in isolation and subsequently their synaptic spread to other networks can be investigated.

Overall, this model for investigating synaptic maturity and tau spread in vitro has the potential to provide new insight into the cellular mechanisms behind neurological disorders such as Alzheimer's disease. It also provides a convenient on-chip platform for investigating novel therapeutics to help prevent the spread of disease.

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Poster number: P-T103
Theme: Neurodegenerative disorders & ageing

Using in vitro systems to study the role of isoform-specific Apolipoprotein E processing in Alzheimer's Disease

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The E4 allele of the Apolipoprotein E (APOE) gene is still the strongest genetic risk factor for sporadic Alzheimer's Disease (AD), whereas the E2 allele of APOE is associated with reduced risk for AD and a later age of onset. The three major ApoE isoforms (ApoE2, ApoE3 and ApoE4) are distinguished by polymorphisms that alter the protein structure and thus function. Although a major role of ApoE in AD involves the modulation of Aß-homeostasis, other mechanisms underlying ApoE-mediated pathology in AD have begun to emerge. Under normal physiological conditions, ApoE is primarily expressed by astrocytes in the brain. However, neurons under stress conditions, which may occur during the early stages of AD, express ApoE. Although this is thought to be a protective response, evidence shows that ApoE undergoes isoform-specific fragmentation in neurons due to different intra- and inter-domain interactions, which generate bioactive fragments that may be toxic. This evidence supports an alternative model, which proposes that ApoE proteolysis in neurons is a key contributor to the development of the disease.

Surprisingly though, very little is known about ApoE processing and the factors that affect it, the identity of the fragments, or the function of ApoE in neurons. Therefore, we examined fragmentation of human ApoE2, ApoE3 and ApoE4 in transfected neuronal-like cells and primary rat neurons under various conditions. Here, we present evidence showing isoform-specific fragmentation for all three ApoE isoforms in vitro. We also show that the fragmentation depends on the model system used. For instance, a 15kDa fragment was unique for ApoE4-expressing primary neurons, but was common for ApoE2 and ApoE4 Neuro-2a cells. Moreover, the composition of ApoE fragments appeared different between neuroblastoma cells and primary rat neurons.

This is of importance because insights into ApoE processing for each isoform may partially explain the different effects these variants have in neurons, but could also provide new targets for preventing the generation of the toxic fragments. Additionally, differences in ApoE processing between cell models highlights the limitations of in vitro model systems in studying ApoE-mediated pathology.

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Poster number: P-T104
Theme: Neurodegenerative disorders & ageing

In vivo imaging of mitochondrial transport deficits in the rTg4510 mouse model of tauopathy

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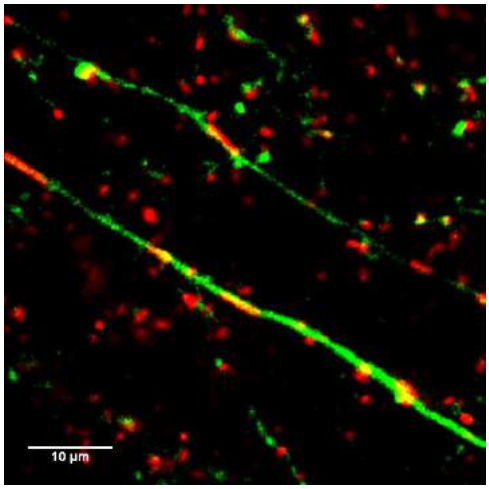
The pathological accumulation of tau is associated with a number of diseases including Alzheimer's Disease (AD). Tau is predominantly a microtubule stabilizing protein, enabling the replenishment and regulation of the key transport route for axonal cargoes. Tau can become hyperphosphorylated, becoming aggregative and toxic, spreading throughout the brain forming intracellular neurofibrillary tangles. Uncovering the functional elements that could underpin the synapse loss and cell death observed in tauopathies is crucial in slowing down or reversing these diseases. Mitochondria are crucial for neuronal health and maintenance of synaptic function, and have been linked to degenerative pathologies. Mitochondrial dysfunction can lead to changes in ATP production, Reactive Oxygen Species deregulation, disruption in calcium buffering and apoptosis control. These dysfunctional pathways can lead to synaptic damage and cell death. The changes and the time course of mitochondrial function and its relationship to synapse loss in tauopathies, AD patients and animal models is not well known. Here, longitudinal in vivo two-photon microscopy is performed in rTg4510 mice, which express a repressible form of human tau containing the potent P301L mutation. rTg4510 mice and control littermates were transduced with an AAV driving expression of cytosolic & mitochondrial-targeted fluorescent proteins in a subset of excitatory cortical neurons. Repeated imaging of the distribution and motility dynamics of axonal mitochondria was performed in head-fixed, anaesthetized mice. These results show the changes in mitochondria occurring with increasing tau pathology. Transgenic mice show decreased chances of motility and in the ratio of motile mitochondria vs total mitochondria. An initial increase in mitochondrial density along the axon is seen in the rTG4510 mice, followed by a decrease against control mice. An increase the pause ratio of the mobile mitochondria is seen along with an increase

in the average pause time. Age related decreases mobile mitochondria speed are also seen in the rTg4510 mice. The data indicates mitochondria may have a key role in the tau related neurodegeneration from an early age.



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Poster number: P-T105
Theme: Neurodegenerative disorders & ageing

Mechanisms of alpha-synuclein induced synaptopathy in a Drosophila model of Parkinson's disease

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Parkinson's disease has been characterised as a synaptopathy that exhibits early synaptic deficits which occur prior to neurodegeneration. However, the mechanisms underlying synaptic dysfunction are largely unknown. Here we investigate mechanisms of α-synuclein induced synaptopathy in a Drosophila model of Parkinson's disease. Using the Gal4/UAS system, we overexpressed wild type and mutant forms of human α-synuclein in a subset of 30 dopaminergic neurons in the protocerebral anterior medial (PAM) dopaminergic cluster in the adult central brain. Video-assisted motion tracking revealed that α-synuclein expression caused impaired motor behaviour characterised by decreased overall activity and speed, accompanied by increased action initiation and decreased maintenance of motor actions. These early behavioural deficits are neither caused by loss of synaptic arborisations nor degeneration of neurons despite accumulation of α-synuclein, thus suggesting synaptic dysfunction as underlying cause. Accordingly, further investigations are under way to determine whether proteins responsible for the maintenance of the active zone of synapses are altered due to the accumulation of α-synuclein. So far, we found decreased expression levels of nicotinamide mononucleotide adenylyltransferase (NMNAT) in adult flies expressing α-synuclein pan-neuronally. NMNAT has been shown to play an essential role in presynaptic terminals by stabilising Bruchpilot (BRP), which is required for structural integrity and function of synaptic active zones in Drosophila. Further analysis revealed that expression of mutant α-synuclein reduced the number of active zones in the presynaptic region of the Drosophila neuromuscular junction and altered Bruchpilot protein levels in larval brain. Taken together, our results suggest that accumulation of α-synuclein impairs the integrity and function of the presynaptic active zone, leading to synaptopathy and the progressive loss of neurons, thus mimicking early onset and progression of Parkinson's disease.

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Poster number: P-T106
Theme: Neurodegenerative disorders & ageing

Attrition in the Brains for Dementia Research Cohort: Withdrawals & Lost Donations

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Objectives: To examine attrition in a cohort of potential brain donors and identify predictors of withdrawal and lost donation.

Methods: Brains for Dementia Research cohort data (gender, age, diagnosis at registration, withdrawals, donations, lost donations) were analysed to determine attrition and to identify reasons for participant withdrawal and unrecovered brain donations. Logistic regression was used to identify participant characteristics that predicted withdrawal and lost donations.

Results: Of 3287 consented participants (Mean age 78.9 years, SD 8.8), to date 643 (19.6%) have died, including 194 (30.2%) healthy 'control' participants. Attrition was 5.8% comprising 105 (3.2%) participants withdrawing during life and 85 (2.6%; 13.2% of deceased) lost donations. Primary withdrawal reasons were 'no reason provided' (38, 36.2%), 'family disagreement' (20, 19.0%) and 'participant changing mind' (17, 16.2%). Reasons for lost donations were 'brain bank not informed' (34, 40.0%), 'Coroner case' (21, 24.7%) and post mortem delay/'No reason provided' (7, 8.2%). Being older (OR=1.04, 95% CI: 1.02-1.07, p=<.001) and a dementia diagnosis (OR=2.15, 95% CI: 1.34-3.37, p=.001) increased risk of withdrawal. Being younger (OR=.97, 95% CI: .95-.99, p=.028) and being a control participant (OR=.36, 95% CI: .22-.59, p<.001) predicted lost donation.

Conclusions: Although attrition was relatively low, for cohorts collecting regular clinical data in life, withdrawal and failure to achieve brain donation represents a significant loss, especially from control participants from whom tissue is scarce and in greatest demand. Strategies to maximise participant retention and to minimise lost donations must reinforce the value of donation and enhance engagement with participants and families. However, this does leave a very large active cohort of participants with serial assessment data available to researchers. Furthermore, with more than 500 participants having already donated their brains, there is an extensive tissue bank of well-characterised samples available.

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Poster number: P-T107
Theme: Neurodegenerative disorders & ageing

Arfaptin 2 regulates cell viability via PI3 kinase/AKT pathway in Amyotrophic lateral sclerosis (ALS)

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Amyotrophic lateral sclerosis (ALS) is a devastating, adult onset motor neuron disease (MND) that has no effective treatment to date. The current study investigates the possibility of targeting protein aggregation pathway for treatment. Modulation of this pathway is approached through targeting Arfaptin2 protein. A dominant negative form of Arfaptin2 (HC-ARFIP2), has been shown to have a neuroprotective property that maintains the proteasome activity and induces degradation of misfolded proteins. We thus proposed that the HC-ARFIP2 improves neuronal survival in ALS via maintaining the proteasomal pathway. Expression of HC-ARFIP2 in primary motor neuron cultures using LV-based vector, improved motor neuron survival significantly. The prosurvival effect was observable even in cells treated with H2O2 in both SOD1G93A transgenic and non-transgenic motor neurons. A further investigation on the pathway of which HC-ARFIP2 exerts its neuroprotective effect showed that HC-ARFIP2 induces Akt phosphorylation. In addition, protein degradation pathway-markers (p62, LC3II, ULK1) showed significant changes in response to HC-ARFIP2 expression. Furthermore, Arfaptin2 showed colocalisation with SOD1 and overexpression of FL-ARFIP2 caused aggregates formation in HEK293T cells compared to HC-ARFIP2 expression that maintained the cytoplasmic distribution of SOD1. In conclusion, the study presented here has provided a proof of concept that Arfaptin2 is involved in protein aggregation in ALS. In addition, HC-ARFIP2 expression can improve motor neuron survival in vitro through activation of Akt and proteasome activity.

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Poster number: P-T108
Theme: Neurodegenerative disorders & ageing

The role of oxidative stress in age-related changes in the Cerebral Giant Cells of the pond snail, Lymnaea stagnalis

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Background: The complexity of the mammalian brain has made it difficult to understand neuronal ageing. As a result, simpler models can be utilised to investigate how neurones age. The invertebrate, Lymnaea stagnalis, is a suitable model due to its relatively simple CNS and ability to perform a top-down approach linking behavioural changes to properties of identified neurones. Importantly, Lymnaea neurones exhibit a number of age-related changes that are observed in mammalian neurons, including reduced excitability and an increase in the afterhyperpolarisation. In this study the mechanisms underlying age-related changes were investigated in the serotonergic cerebral giant cells (CGCs) in Lymnaea.

Methods: Current clamp experiments were performed on CGCs from young (3-4 month old) and old (8-9 month old) Lymnaea. To investigate the role of oxidative stress in neuronal ageing, a group of young Lymnaea CNSs were treated extracellularly with the pro-oxidant generator, 2'-azobis (2-amidinopropane) hydrochloride (AAPH). A lipid peroxidation assay was performed on CNSs to determine malondialdehyde (MDA) levels.

Results: Intracellular recordings revealed a decrease (approximately 50%) in spontaneous firing frequency and a significant increase in the amplitude and duration of the afterhyperpolarisation in both old and AAPH treated CNSs when compared to young controls ($p<0.01$). Spike frequency adaptation was observed in old CGCs but there was no alterations in SFA in AAPH-treated cells ($p>0.05$). Interestingly, experiments with AAPH also revealed that decreased firing caused by a low concentration of 3 mM was irreversible and due to lipid peroxidation. Conversely, the effects of 10 mM AAPH on firing was reversible and not associated with elevated MDA levels ($p>0.05$). The protective effect of 10 mM AAPH on MDA levels was blocked by perfusing CGCs with TEA, a potassium channel blocker ($p<0.001$).

Conclusion: Extracellular AAPH induces alterations in young CGCs that are largely consistent with age but at low concentrations does so by imparting a pro-oxidant effect and at higher concentrations may confer neuroprotection possibly via the modulation of potassium channels. Future experiments will involve studying potassium currents with age and AAPH in voltage clamp.

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Poster number: P-T109
Theme: Neurodegenerative disorders & ageing

Molecular profiling of differentially vulnerable synaptic populations and in-vivo phenotypic assessment identifies regulators of neuronal stability

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Synapses are an early pathological target in a wide range of neurodegenerative conditions including well-known adult onset Alzheimer's, Parkinson's and Huntington's disease [1-3] and diseases of childhood such as the motor neurone disease - Spinal Muscular Atrophy and the neuronal ceroid lipofuscinoses (NCLs; A.K.A Batten disease) [4-6]. However, our understanding of the mechanisms regulating the stability of synapses and their exceptional vulnerability to neurodegenerative stimuli remains in its infancy.

To address this we are using the NCLs as a tool to identify novel regulators of synaptic stability, contributing to our understanding of a broad range of diseases and highlighting novel therapeutic targets. The NCLs, are the most frequent autosomal-recessive disease of childhood [7]. There are currently 14 individual genes which mutations are capable of affecting lysosomal function, all of which result in similar phenotype including blindness, cognitive/motor deficits, seizures and premature death. Mutations in CLN3 underlie

a juvenile form of NCL (JNCL or CLN3 disease), the most prevalent variant worldwide [8]. Differential vulnerability of distinct synaptic populations across different brain regions has been described in other models of NCL variants [5, 6] but not yet in JNCL.

Here, we describe a similar pattern of synaptic loss in the Cln3 null mouse model of JNCL (Cln3-/-). Secondly, we use this differential pattern of synaptic loss to map molecular expression profiles across three brain regions. Thirdly, this region vulnerability expression mapping revealed conserved molecular alterations between JNCL and other neurodegenerative conditions [9]. Finally, we demonstrate that genetic and/or pharmacological manipulation of candidate expression in Drosophila is sufficient to modulate disease progression in-vivo.

1. DeKosky ST et al. Ann Neurol., 1990
2. Forno LS et al. J. Neuropathol. Exp. Neurol, 1996
3. Murphy KP et al. Neurosci, 2000
4. Murray LM et al. Hum Mol Genet, 2008.
5. Kielar C et al. Hum Mol Genet, 2009.
6. Partanen S et al. J. Neuropathol. Exp. Neurol., 2008
7. Goebel, HH, J. Child. Neurol, 1995
8. Palmer DN. et al. Biochim Biophys Acta, 2013
9. Wishart TM et al. PLoS Genet, 2012.

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Poster number: P-T110
Theme: Neurodegenerative disorders & ageing

Reducing the response to DNA damage protects against neurodegeneration

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Double-strand DNA breaks (DSBs) are the most deleterious form of DNA damage. In young mouse brains they are generated and repaired quickly as part of normal learning but accumulate in the brains of Alzheimer's disease model mice. DSBs also accumulate in the early stages of Alzheimer's disease and correlate with reduced cognitive function. We are investigating whether the response of neurons to DNA damage contributes to pathology in neurodegeneration.
We have used genetic methods to reduce the activity of the MRN complex, the evolutionarily conserved tri-partite complex required for detection of DSBs in all cells. We applied the technique to Drosophila models of Alzheimer's disease, fronto-temporal dementia and Huntington's disease. We used a standard method of assessing general neural function in these fruit fly models based on quantifying the negative geotaxis of flies as they age and show that reducing MRN complex activity dramatically suppresses neuropathology in each model.
Given the MRN complex is so highly conserved and that reducing activity is neuroprotective in three different models of neurodegeneration, our data suggest small molecular inhibitors of MRN are a potential new therapeutic target to slow neuropathology. We have developed an in vivo screening platform based on our Drosophila assay to test a new library of second-generation targeted small molecule inhibitors of the MRN complex. Compounds emerging that suppress neuropathology will be candidates further testing in vertebrate models of neurodegeneration. We have already identified one protective compound in initial screening and will present updated findings.

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Poster number: P-T111
Theme: Neurodegenerative disorders & ageing

Interactions of Genes Causing Parkinson's: Evaluation of Visual Phenotypes

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Background: Parkinson's Disease (PD) is a common, progressive neurodegenerative condition with an estimated prevalence of 160 people per 100 000. Approximately 15% of PD is familial or genetic. Although PD is primarily considered a motor disorder, visual changes include reduced visual acuity and reduction in colour vision discrimination. PD patients have reduced dopamine within retinal cells. The fruitfly, Drosophila melanogaster is a useful model for studying PD as both the human and Drosophila visual

systems contain dopaminergic neurons. Electroretinograms (ERG) and steady state evoked potentials (SSVEP) have been used to examine the visual system in both humans and flies, with high fidelity readout.

Hypothesis: We aim to test for interactions between Parkinson's disease related genes. If they are in the same genetic pathway, we would expect to find a more severe phenotype in double mutants, and be able to rescue the phenotype by increased gene expression.

Methods: Crosses were made between adult male flies and virgin female flies to create the required Drosophila genotypes. Flies aged 24 hours were aspirated into pipette tips, and restrained. Glass electrodes containing simple Drosophila saline solution were placed on the surface of the fly's eye to record response and in the fly's mouth as a control. ERGs and SSVEPs were carried out using flickering light and response recorded. N=270.

Results: The double mutant TH>Lrrk2-G2019S/parkinz3678 has a worse ERG phenotype than the single mutant (p=0.029), which the SSVEP analysis suggests is due to neural signalling deficits. Expression of PINK1 (TH>Lrrk2-G2019S>PINK1) rescued the visual deficit (p=0.024), but attempted rescue with parkin (TH>Lrrk2-G2019S>parkin) or DJ1 (TH>Lrrk2-G2019S>DJIA) appears to only partially rescue the phenotype, (p=0.46, p=0.12,) due to the small numbers of flies.

Conclusion: Our data suggests that DJ1, PINK1 and Lrrk2 genes are in the same cellular pathway phenotype and suggests that drugs developed for one genetic form of PD may also benefit other patients with genetic PD or even those with idiopathic PD.

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Poster number: P-T112
Theme: Neurodegenerative disorders & ageing

Developmental stress and ageing brain

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Ageing is a complex process influenced by many factors. This project focuses on how stress affects brain ageing. It is well known that having a stressful environment during development induces permanent physiological changes in the organism to maximise survival (e.g. faster growth1 and altered stress hormone receptor expression in the brain2). However, it is not well known how developmental stress influences the ageing trajectory or which developmental period is most crucial for this effect.
Whilst ageing varies hugely between species, there appears to be many shared mechanisms, such as the accumulation of oxidative end products. In time I aim to test the similarities and differences in brain ageing across taxa and the consequences of developmental stress for different animal groups. The data presented here is derived from work on a novel in vitro model of aged human neurons, which has been developed in our lab group. The data demonstrates that with time in culture these neuronal cells accumulate biomarkers of ageing such as increased protein oxidation, lipid peroxidation and decreased antioxidant capacity. Furthermore these cells were manipulated by exposure to a variety of concentrations of cortisol to mimic chronic stress and the consequences of this for the ageing trajectory are presented and discussed. In conclusion, it is clear that stress influences how we age but that this differs across models of ageing.

1. Amugongo, S. K., & Hlusko, L. J. (2014). Impact of Maternal Prenatal Stress on Growth of the Offspring, 5(1), 1–16.
2. Zimmer, C., & Spencer, K. a. (2014). Modifications of Glucocorticoid Receptors mRNA Expression in the Hypothalamic-Pituitary-Adrenal Axis in Response to Early-life Stress in Female Japanese Quail. Journal of Neuroendocrinology, 26(12), 853–860.

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Poster number: P-T113
Theme: Neurodegenerative disorders & ageing

Behavioural and Neurochemical Alterations Associated with Normal Aging in the Rat

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterised by a wide range of cognitive and behavioural alterations including memory loss and apathy. Advancing age is one of the biggest risk factors for AD and as such, its prevalence is expected to increase as a consequence of the steady growth of the aging population. Normal aging and age-related diseases are usually accompanied by cognitive decline and structural alterations in brain areas such as the hippocampus and cortex. Converging evidence suggest that age-related GABAergic alterations in the hippocampus and prefrontal cortex may lead to deficits in spatial reference and working memory tasks respectively, while alterations to dopamine signalling pathways may be responsible for alterations in reward learning and motivation.

The present study aimed to investigate whether aged (15-20 months) male Sprague-Dawley rats exhibit any of the behavioural and neurochemical alterations previously associated with normal aging as compared with young (3-8 months) rats. Cognitive and behavioural functions were assessed using Y-maze spatial reference memory, T-maze delayed alternation, and progressive ratio schedule of reinforcement tasks. Neurochemical alterations were investigated at 22 months of age following behavioural testing in the dorsal hippocampus and the nucleus accumbens.

The aged rats performed significantly worse in both the Y-maze spatial reference memory and the progressive ratio tasks. No deficit was observed in the rewarded T-maze delayed alternation paradigm. Behavioural alterations were associated with age-related alterations in GABA neurotransmission in the dorsal hippocampus and DA neurotransmission in the nucleus accumbens as well as reduced DA, DOPAC and HVA basal levels in the aged rats. No other alterations in neurotransmitter function or basal levels were observed in either the dorsal hippocampus or the nucleus accumbens.

Such disruptions to key neuronal pathways in normal aging could be a reflection of the underlying dysfunctional mechanisms and circuits that contribute to symptom onset in AD. Future studies will extend neurochemical profiling to other brain regions to better understand age-related circuit and network dysfunction that may be beneficial to AD research.

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Poster number: P-T114
Theme: Neurodegenerative disorders & ageing

Mitochondrial deficit in a novel tau transgenic mouse model of human tauopathy

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Neurodegenerative diseases in which tau isoforms containing four microtubule-binding repeats (4R) are overrepresented, such as progressive supranuclear palsy, contain an N-terminally truncated form of tau (Tau35) that is absent from age-matched control brain. We have generated a new mouse model of tauopathy expressing Tau35, in the absence of any mutation and under the control of the human tau promoter (Bondulich et al., 2016). Unlike most existing tau transgenic mice, expression of Tau35 in these animals comprises less than 10% of endogenous mouse tau, which is comparable with tau expression in human neurodegenerative disease. Importantly, Tau35 mice demonstrate key features of human tauopathy, including aggregated and abnormally phosphorylated tau, progressive cognitive and motor deficits, altered protein kinase activity, loss of synaptic proteins, and reduced life-span. Western blots of mouse brain homogenates revealed a reduced amount of the mitochondrial marker, heat-shock protein 60 (HSP60) in Tau35 mice, compared to wild-type mice. To investigate the influence of Tau35 expression in neurons, we examined mitochondrial morphology and mobility in primary cortical neurons cultured from Tau35 and wild-type mice. In order to assess mitochondrial mobility, neurons were co-transfected with plasmids expressing (1) the mitochondrial targeting protein, cytochrome c oxidase, fused to DSRed2 and (2) enhanced green fluorescent protein. Live recording of mitochondria in cultured neurons identified a significant reduction in the total number of mitochondria present in neurites of neurons prepared from Tau35 mice, compared to those derived from wild-type mice. However, the percentage of moving mitochondria was similar in both Tau35 and wild-type neurons. The results suggest that defective mitochondrial function may be critically involved in the development and progression of tauopathy in Tau35 mice. This emulation of disease pathogenesis in neurons derived from a novel mouse model will aid identification of the molecular changes that cause neurodegeneration in the human tauopathies.

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Poster number: P-T115
Theme: Neurodegenerative disorders & ageing

The role of neuroinflammation in the pathology of P301S tau transgenic mice

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Alzheimer's disease (AD) is the most common age-related dementia. Neuroinflammation plays a key role in the pathophysiology of neurodegenerative diseases, including AD. In this study we assessed the contribution of the neuroinflammatory response to the pathology associated to tau hyperphosphorylation and accumulation. We used transgenic mice expressing human P301S tau protein that exhibit many characteristics of the human tauopathies, including the formation of abundant hyperphosphorylated tau protein filaments and neurodegeneration. We found that P301S mice develop predominant spinal cord pathology, with altered locomotion. Tau accumulation is evident in spinal motoneurons at 6 weeks of age, leading to cell degeneration from 12 weeks of age. This is accompanied by a significant expansion of the microglial population and increased expression of pro-inflammatory cytokines, with no evidence of a contribution from infiltrating cells. Overall, our findings demonstrate that neuroinflammation significantly contributes to the pathology in P301S mice, and suggest that strategies aiming at controlling this process may represent a promising therapeutic perspective.

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Poster number: P-T116
Theme: Neurodegenerative disorders & ageing

The effect of aggresomes on centrosome and cilium function

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Background: Aggresomes are closely related to Lewy bodies (LBs), structures whose presence is a hallmark of Parkinson's disease. LBs are related to aggresomes. A major constituent of these LBs is alpha synuclein, the gene for which is mutated in the inherited form of Parkinson's. The cellular location of aggresomes coincides with that of the centrosome, the microtubule organising centre of the cell. Since the aggresome is positioned in close proximity to and shares components with the centrosome, it is possible that it hinders centrosomal function. If that is the case it could in turn affect intracellular transport and cell polarity, both of which are very important for neuronal function and survival.

Objectives: In this study we sought to test if any functions of the centrosome were impeded by the presence of aggresomes in their close vicinity.

Methods: Several cell lines including SH-SH5Y, HeLa cells and primary rat neurons were treated to induce aggresomes. This was achieved either by exposure to the proteasome inhibitor MG-132 or by transfection with alpha synuclein overexpression constructs. Centrosome function was assessed by microtubule regrowth, wound healing and ciliogenesis assay. Similarly zebrafish embryos were exposed to MG-132 were cilia at the olfactory neurons were stained for.

Results : We show here that aggresomes severely compromise centrosome function. Microtubule nucleation is severely reduced and the centrosome is unable to be repositioned during cell migration. We also show that aggresomes can prevent a cell from turning its centrosome into a cilium. Also in zebrafish embryos number of cilia in the olfactory epithelium is severely reduced.

Conclusion: Defects in the generation and organisation of the microtubule network would be predicted to affect intracellular transport. As well as the deleterious effects on core vesicular trafficking, the inability to move vesicles involved in neurotransmitter transport through the cell would be particularly problematic for neurons. An early symptom of Parkinson's is loss of smell and

anosmia. It maybe possible this symptom is a result of loss of cilia from olfactory neurons. If this is the case, then cilia density in the olfactory epithelium of Parkinson's patients should be reduced.

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Poster number: P-T117
Theme: Neurodegenerative disorders & ageing

An exploration into the behaviour of myelin proteins during myelin injury

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Current knowledge of the structure of myelin has been mainly derived from the use of static electron micrographs, although these are useful to derive structural information, these do not provide the needed information to understand the behaviour of myelin during dynamic events such as the formation and repair. Understanding of these events relies upon more comprehensive direct observation of the microenvironments. Typically, these observations involve the use of conventional ensemble –averaged imaging of the molecular properties within the system. However, these ensemble-averaged observations can fall short when observing events which only occur in a sub-population of the system. In order to derive information on these events the full probability distribution of the different states of the molecules need to be observed, providing a need for single molecule imaging.

To aid in this observation a fluorescent construct was designed using a photoswitchable fluorescent protein bound to myelin basic protein, which was instilled in the semliki forest virus. This virus was used to infect Oligodendrocytes within both brain slices and within the Oli Neu cells, oligodendrocyte cell line. Images were obtained over a 5-minute interval on a TIRF microscope, and were analysed using single molecule analysis software. Analysis of particle tracks revealed that MBP diffuses around processes within Oli Neu cells, which do not have the complement of proteins a mature oligodendrocyte cells contain, however, results thus far suggest this is not the case when observing mature cells.

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Poster number: P-T118
Theme: Neurodegenerative disorders & ageing

Interaction between alpha-synuclein aggregation and inflammatory responses in Parkinson's Disease

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Presence of cytoplasmic protein aggregates called Lewy Bodies (LBs) in the brain of Parkinson's disease (PD) patients represents one of the main pathological hallmarks. These aggregates are composed of α-synuclein, an abundant presynaptic protein critical for synaptic transmitter release. LBs have been linked with neuronal loss, microglia activation and neuroinflammation. In addition, mounting evidence suggests that the humoral immune response driven by T lymphocyte plays a role in disease progression in PD. Previously reported is the putative influence of alpha-synuclein on the adaptive immune response, which involves the infiltration of cytotoxic CD4 and CD8 positive T-cells in the substantia nigra, and leads to the subsequent activation of these cells and the production of pro-inflammatory cytokines. A long term corollary then is the accumulation of neurotoxins and eventually the neurodegeneration of neurones. In the present study we focused our attention on the presence of LBs and alpha synuclein in post-mortem brain tissue from PD patients; once these were recognised, we explored the presence and compartmentalisation of immune cells, in particular, microglia and T-lymphocytes, in the vicinity of aggregates.
Paraffin embedded brain human tissue from PD patients (striatum and substantia nigra) obtained from the MS and Parkinson's Tissue Bank (Imperial College London) was analysed through immunohistochemistry. Immunostaining was performed on 5 µm-thick sections, incubated with different primary antibodies for 48h at 4°C. Biotinylated secondary antibodies were amplified and immunostaining confirmed using 3,3'-diaminobenzidine tetra-hydrochloride (DAB). These yielded clear synuclein-containing cell labelling in both the soma and processes of striatal neurones. These are most likely medium spiny neurones diffusely localised in the striatum. We currently explore the presence of immune cells through double labelling with T-cell specific antibodies. These preliminary qualitative data confirm the presence of pathological alpha synuclein and T-cells in the brain parenchyma of PD patients. Future work will seek to establish a correlation between α-synuclein and inflammatory response using the injection of patient-extracted LBs into the brain of mice as a model.

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Poster number: P-T119
Theme: Neurodegenerative disorders & ageing

Identification of novel biomarkers for the improvement of the diagnosis, prognosis and treatment of multiple sclerosis

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Multiple Sclerosis (MS) is a complex immune-mediate disease of the CNS, characterized by demyelination, axonal damage and scar formation. MS is one of the most widespread disabling neurological conditions around the world with more than 2 million people being affected. It includes several clinical subtypes, with the most common form being Relapsing Remitting MS (RRMS). Due to the heterogeneity of clinical presentation, MS is difficult to diagnose and therefore efforts have been directed towards the identification of biomarkers to facilitate diagnosis and improve treatment, but despite the large number proposed, only few are currently used for clinical purposes. The aim of this study is to identify molecules that can be measured in blood and provide a simple and cost-effective tool for improving MS diagnosis and treatment, as well as delineating between the MS subtypes.
For our initial investigation, we performed a gene expression analysis on a pilot set of blood samples obtained from RRMS patients and age- and gender-matched controls (n=20) using the Affymetrix GeneChip Human Transcriptomic Array 2.0. We identified 8721 significantly differentially expressed genes ($p \leq 0.05$) that were then analysed through Ingenuity Pathway Analysis (IPA) to explore associated functions and pathways. We then employed a combination of qPCR and HPLC/Mass Spectrometry in a larger sample set to validate and further investigate our data.
We have identified a subset of molecules that are differentially expressed in RRMS and may present novel targets for MS diagnosis and treatment. These candidates include molecules involved in neurological and inflammatory processes, as well as novel targets such as microRNAs. For example, DEFA4, an antimicrobial peptide known to promote local inflammation, was significantly up-regulated, while NOTCH1, which mediates oligodendrocytes differentiation and remyelination, was significantly down-regulated.
The identification of MS biomarkers in the blood could facilitate an early diagnosis, allowing clinicians to apply treatment strategies more effectively. The MS-related molecules identified in this study, in fact, could be used to discriminate between MS and other inflammatory diseases and could potentially function as novel targets for drug development.

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Poster number: P-T120
Theme: Neurodegenerative disorders & ageing

A bioluminescence reporter assay to select RARα specific drugs that control translation of the GluR1 subunit of the AMPA receptor

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Nuclear receptors comprise a major group of signalling pathways in the brain. They have a well described mechanism of action to regulate gene expression. Additional “non-genomic” roles exist for many of these receptors such as the retinoic acid receptor alpha (RARα). Retinoic acid mediates a type of homeostatic plasticity by regulating the translation of the GluR1 subunit of the AMPA receptor through RARα (1). In the absence of retinoic acid, RARα binds with GluR1 mRNA directly preventing its translation. During synaptic scaling, blockade of synaptic activity triggers retinoic acid synthesis which in turn binds to RARα and releases the GluR1 mRNA to be translated which causes an increase in the postsynaptic AMPA receptor levels. Retinoic acid also regulates AMPA receptor trafficking (2).
The question was asked whether this non-genomic activity of RARα could be disassociated from its action as a transcription factor and whether different ligands for RARα may preferentially activate one pathway or the other. A bioluminescence reporter plasmid that expresses firefly luciferase under the control of the GluR1 5’ untranslated region was constructed and introduced into SH-SY5Y cells. The cell line is being used to screen synthetic retinoids for their ability to increase AMPA receptor translation versus activation of gene transcription. The results will indicate whether RARα ligands may be selected of high specificity for their capacity to increase AMPA receptor levels and which may provide therapeutics with fewer side-effects for disorders that result in cognitive loss, including Alzheimer’s disease (3).

1. Aoto J, Nam CI, Poon MM, Ting P, Chen L. Synaptic signaling by all-trans retinoic acid in homeostatic synaptic plasticity. Neuron. 2008 Oct 23;60(2):308-20
2. Arendt KL, Zhang Y, Jurado S, Malenka RC, Südhof TC, Chen L. Retinoic Acid and LTP Recruit Postsynaptic AMPA Receptors Using Distinct SNARE-Dependent Mechanisms. Neuron. 2015 Apr 22;86(2):442-56
3. Chakrabarti M, McDonald AJ, Will Reed J, Moss MA, Das BC, Ray SK. Molecular Signaling Mechanisms of Natural and Synthetic Retinoids for Inhibition of Pathogenesis in Alzheimer's Disease. J Alzheimers Dis. 2016;50(2):335-52.

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Poster number: P-T121
Theme: Neurodegenerative disorders & ageing

Altered PTGS2 expression characterises the cortex and cerebellum in Parkinson's disease

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Prostaglandin-endoperoxide synthase (PTGS) catalyses the first step in the synthesis of prostanoids; consisting of prostaglandins, prostacyclin and thromboxanes. Both constitutive and inducible isoforms exist. PTGS2 is the inducible isoform, which is dramatically upregulated in response to pro-inflammatory molecules. Several lines of evidence point towards neuroinflammation as critical to the pathophysiology of Parkinson's disease (PD). Epidemiological studies suggest risk reduction of PD with non-steroidal anti-inflammatory drug use. Inhibition of PTGS2 is neuroprotective in animal models of PD. Here, we quantified the expression of PTGS2 by Western blotting in mitochondria of post-mortem cortex tissue of individuals with PD and age and Braak stage matched controls. Further, we investigated the cerebellar cellular localisation of PTGS2 expression using immunohistochemistry. Our data suggest that PTGS2 levels are elevated in the cortex of individuals with Parkinson's disease and distinct changes in the cerebellar cellular localisation of PTGS2 expression exist. We will present our latest work aiming to determine whether changes in PTGS2 are driving, or a consequence of Parkinson's disease.

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Poster number: P-T122
Theme: Neurodegenerative disorders & ageing

Probabilistic casual model based assessment optimization for Alzheimer's disease diagnosis

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From a practical standpoint, biomarker data such as genetics and brain imaging are less economical or not commonly obtained in typical dementia care. Further, some assessments can take too long to evaluate within limited consultation time. This study aims to focus on more easily accessible data to obtain an optimal set of assessments for an individual by balancing classification accuracy and time spent.

Our previous work using the Australian Imaging Biomarkers and Lifestyle flagship study of ageing (AIBL) has shown that psychological/functional assessments provide higher classification accuracy than other data features. Hence, we emphasize on the clinical dementia rating (CDR), mini-mental state exam (MMSE), logical memory immediate/delayed recall (LMIR/LMDR) assessments, age, and 2 significant medical histories: neurologic history (NEURL) and renal history (RENAL). We first used Bayesian network (BN) modelling approach to identify probabilistic causalities among various data types. While applying 10-fold cross validation, a synthetic minority over-sampling technique was used to balance the unbalanced training data due to uneven proportion of diagnostic categories. The obtained BN showed a sensitivity of 0.79 and specificity of 0.97 for AD diagnosis, and the total accuracy of 0.89 for all classes of diagnosis. Diagnostic result was most strongly linked to CDR, followed by LMDR, MMSE, and LMIR.

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Poster number: P-T123
Theme: Learning & memory

The retrosplenial cortex and object recency memory in the rat

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The current experiments examined the role of the retrosplenial cortex in distinguishing the temporal order of events (i.e. recency memory). In Experiment 1, rats with lesions in the retrosplenial cortex (RSC) were tested on two types of recency memory task: Between-Block (i.e. objects were presented in two discrete blocks) and Within-Block (i.e. objects were presented in a continuous series). The RSC group were able to discriminate old from recent objects in the Between-Block condition but not in the Within-Block condition. In Experiment 2, the expression of the immediate-early gene c-fos in retrosplenial cortex was compared between groups of intact rats following either the completion of a between-block recency task or a control task. There were strong, positive correlations between discrimination performance and the levels of c-fos expression in both the granular and dysgranular retrosplenial cortex. Expression of c-fos in the granular retrosplenial cortex also correlated with expression in related areas, such as the ventral subiculum and prelimbic cortex. Taken together, the pattern of results supports a role for the retrosplenial cortex in both between-block and within-block recency problems. Furthermore, when viewed in the context of previous findings, these results suggest that the rat retrosplenial cortex is part of a group of anatomically and functionally connected regions, including the hippocampal formation, medial diencephalon, and medial frontal cortex, that work together to support recency memory.

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Poster number: P-T124
Theme: Learning & memory

Long-term effects of low-dose radiation during early postnatal development on the spatial learning behaviour in C57BL/6 mice

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Present-day medicine takes advantage of modern radiation diagnostics like computer tomography (CT) or curative and palliative radiotherapy, respectively. These treatments are also increasingly used in young children, although their developing brain is exposed to low dosages of radiation. Already after doses of about 50 mGy, as it is used in CT scans of the head, it is possible to detect DNA double-strand breaks in the brain (Saha et al. 2014). We are able to predict long-term effects of an in utero irradiation with higher dosages (> 1 Gy) relatively well from atomic bomb survivors of Hiroshima and Nagasaki (Otake and Schull 1998). Besides the carcinogenic risk, various sequelae like abortion, malformations or mental retardation dependent on the developing status of the embryo during irradiation can occur. Especially, impaired cognitive function could already emerge from dosages < 1 Gy, which is of great social relevance. Consequences of postnatal irradiation on cognitive abilities are less well known and there is still need of information and clarification existing. European radiation protection authorities have encouraged research activities for this issue (Averbeck 2013). Here, we demonstrate the long-term effects on spatial learning behaviour in C57BL/6 mice whole-body irradiated (x-rays) during postnatal brain development (postnatal day 10) and analyzed at 2 months of age. We show that a 500 mGy radiation dose led to longer swimming paths, increased escape latencies and decreased percentage of spatial searching strategies in the Morris Water Maze. Moreover, probe trial tests revealed diminished retention times in the target quadrant and increased distances to the former platform position. Differences to control group were not based on altered motor coordination or fear/exploration behaviour, as demonstrated in the Rotarod and Elevated Zero Maze. Besides further doses, current immunohistochemical analyses of brain sections are designed to reveal possible effects on the neurogenic niche in the dentate gyrus. We suppose that the vulnerability of postnatal brain development is caused by disturbance of the local proliferative microenvironment through low-dose radiation, resulting in the manifestation of hippocampus dependent cognitive impairment in later life.

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Poster number: P-T125
Theme: Learning & memory

N-Cadherin abundance, local protein synthesis, and plasticity mechanisms in dendrites

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Leading theories of learning and memory propose that the strengthening of specific synapses involves communication between pre- and post- synaptic terminals and local protein synthesis. Neuronal cadherin proteins (N-cadherin) have been implicated in synaptic plasticity due to their trans-synaptic localization, persistent expression at mature synapses, and ability to recruit AMPA receptors to the post-synaptic membrane. One of the properties of polyribosomes, the site of local protein synthesis in neuronal processes, is that they move into dendritic shafts and spines in response to plasticity events. Based on this information, we hypothesised that N-cadherin abundance at synapses could be used as an indicator of early plasticity protein synthesis. Using differentiated neuronal human cell lines and fixed human brain tissue, we performed immunofluorescent (IF) staining and confocal microscopy to visualise localization and measure the abundance of N-cadherin and ribosomal proteins at dendritic spines. Furthermore, we explored protein expression patterns in differentiated cells treated with protein translation inhibitors. Visualising these cells and quantifying N-cadherin at dendritic spines provided information about the sequence of events in post-synaptic plasticity. This study presents further support for a role for N-cadherin in synaptic plasticity and raises additional questions about the molecular mechanisms through which cellular adhesion proteins may impact upon learning and memory processes.

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Poster number: P-T126
Theme: Learning & memory

The role of DNA methylation in Lymnaea memory

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Lymnaea stagnalis is a model organism for investigating learning and memory formation. Its aerial respiratory behaviour can be operantly conditioned and the resulting memory can be traced to a well-characterized neuronal network. This memory is enhanced by various environmental stressors including detection of a predator and increased environmental temperature (i.e. thermal stress). Similar to conditioned behaviours in mammals, this memory can be both reconsolidated and extinguished. Additionally, there is evidence for the conservation of various cellular and molecular processes (e.g. protein phosphorylation, retinoid signaling) between vertebrates and invertebrates. Recently, epigenetic changes (e.g. DNA methylation) have been investigated as modulators of memory formation. Interestingly, DNA methylation is required for stress-induced memory enhancement in Lymnaea. Specifically, treatment with a methylation inhibitor (5-AZA) 1 hour before exposure to i) the scent of a predator or ii) a thermal stress, prevents memory enhancement. Here, we aimed to determine how long the memory-inhibiting effect of 5-AZA persists. Animals were treated with 5-AZA 24 hours before exposure to the scent of a predator or a thermal stressor and were then operantly conditioned. Neither group of animals displayed memory enhancement, indicating that the action of 5-AZA persists for at least 24 hours. We next aimed to further describe the involvement of DNA methylation in 'normal' (i.e. non-enhanced) memory. In order to examine whether DNA methylation is required for memory reconsolidation Lymnaea were treated with 5-AZA immediately before memory reactivation. All animals demonstrated memory reconsolidation, suggesting that DNA methylation is not necessary for the reconsolidation of 'normal' memory. Thus, DNA methylation appears to be necessary for memory enhancement, but not for the expression or maintenance of 'normal' memory. Together, these studies further elucidate the involvement of epigenetic changes in invertebrate memory and provide insight into the conservation of these mechanisms between vertebrate and invertebrate species.

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Poster number: P-T127
Theme: Learning & memory

Memory Encoding and Beta De-synchronisation in Parkinson's Disease

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Parkinson's disease (PD) is classified as a movement disorder. However there is an increasing awareness of the significant non-motor burdens experienced by patients. For example PD patients experience cognitive difficulties, including memory deficits. As such there is a pressing need to better categorize and investigate the nature of these deficits, to guide the development of interventions that might ameliorate them. Electrical activity recorded from the brains of PD patients is excessively synchronised within the beta range (13–30Hz) compared to healthy controls. Evidence suggests that abnormal beta synchronisation is the cause of at least some of the motor symptoms of PD. However almost nothing is known about the relationship between the increase in beta activity and non-motor symptoms. Our research investigates whether there is a direct relationship between hyper-synchronised beta activity and the memory deficits experienced in PD. It has been shown in healthy adults that a greater amount of beta de-synchronisation occurs during deep-encoding for words that are subsequently better remembered than for words that are not. It is thought that this beta de-synchronisation is necessary for successful encoding to form a memory of the word. We hypothesised that hyper-synchronisation in the brains of people with PD prevents the necessary de-synchronisation of beta oscillations during encoding and therefore interferes with memory formation. Electroencephalography was recorded during an established memory-encoding paradigm to examine the brain activity of PD patients and healthy controls during memory formation. We will report on the ability of PD patients to recollect words placed in memory compared to healthy controls. We will also report on the association between the ability to remember words and the extent of beta de-synchronisation during deep-encoding. This will be the first presentation of preliminary findings from a novel, timely and important investigation into the relationship between hyper-synchronised beta activity and the memory deficits experienced in PD. If such a relationship exists, this evidence would lend further weight to the hypothesis that hyper-synchronised beta activity is causal to the symptoms of PD.

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Poster number: P-T128
Theme: Learning & memory

Voxel-level functional connectivity of the human amygdala

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The use of large-scale data in neuroscience, for example functional neuroimaging studies with 1,000 participants, is important in enabling understanding of how brain systems operate in health and disease, by allowing voxel-level resolution (Cheng, Rolls et al 2016, Rolls 2016). Here we extend this approach to the analysis of the voxel-level functional connectivity of a brain structure with all other voxels in the brain in a large dataset of healthy humans. In this investigation we measured the resting state functional connectivity (the Pearson correlation) between every amygdala voxel (3x3x3 mm) with every other voxel in the brain in 488 healthy participants. Significant functional connectivities between every pair of voxels were corrected for multiple comparisons (Bonferroni or FDR). It was found that the amygdala has significant functional connectivity in humans not only with some expected regions including the medial and lateral orbitofrontal cortex, pregenual, subgenual and supracallosal anterior cingulate cortex; superior, middle and inferior temporal gyrus; medial temporal lobe regions including the perirhinal cortex; but also with the precuneus. The latter is of interest, for its functional connectivity of the precuneus with the lateral orbitofrontal cortex is increased in depression (Cheng, Rolls et al 2016), and we have now report that the functional connectivity of the amygdala with the precuneus is increased in depression. The method also shows which voxels in the amygdala have functional connectivity with different cortical areas, and some topological organization is evident, in that for example the medial orbitofrontal cortex and precuneus have significant functional connectivity with different but partly overlapping voxels in the amygdala. The approach described here provides a way of analyzing and understanding the connectivity of the healthy human brain at the voxel level.

Rolls,E.T. (2016) Cerebral Cortex: Principles of Operation. Oxford University Press: Oxford.
Cheng, W., Rolls,E.T., Qiu, J., Liu, W., Tang, Y., Chang, M., Wang, XF., Jie,Z., Lin, W., Zheng, L., Pu, JC., Tsai, S-J., Yang, A.C., Lin, C-P., Wang, F., Xie, P. and Feng,J. (2016) Orbitofrontal cortex circuits change in depression. Brain 139: 3296-3309.

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Poster number: P-T129
Theme: Learning & memory

Abnormal activation of the dorsal attentional network in memory impairment after traumatic brain injury

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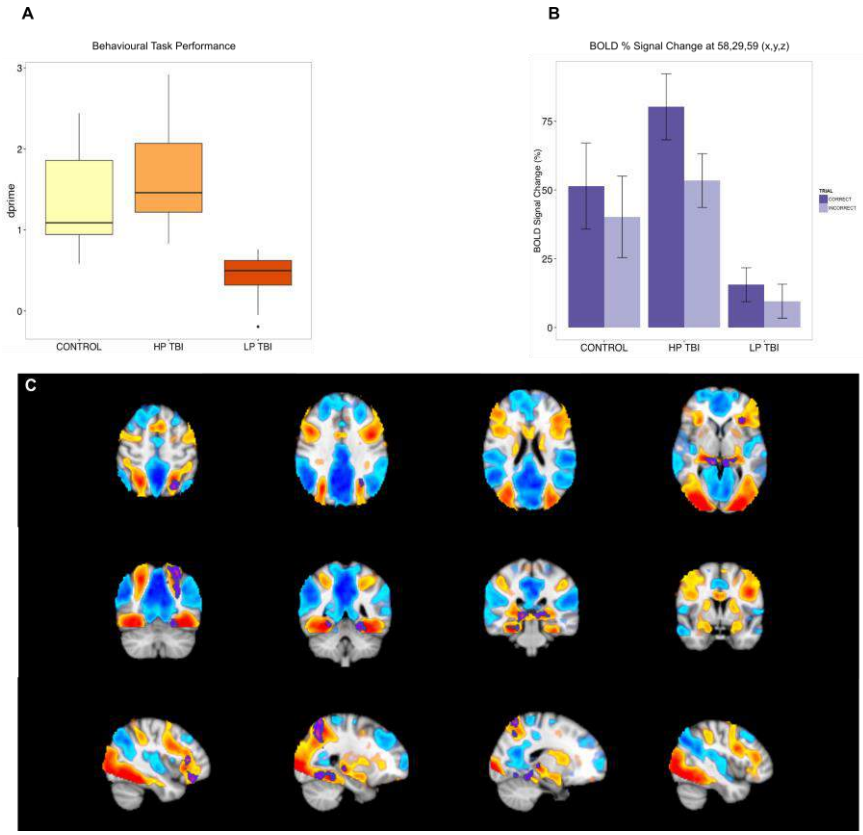
Introduction
Memory deficits are a common cognitive consequence of traumatic brain injury (TBI), and are characterised by abnormal encoding (1). Successful encoding in healthy individuals is associated with recruitment of the dorsal attention network (DAN) and suppression of the default mode network (DMN) (2). TBI patients show abnormalities in the activity of these networks (3) and their interactions (4). We investigated the neural correlates of successful encoding in healthy controls and TBI patients, hypothesising that memory impairment following TBI would be associated with abnormal BOLD signal within the DAN and/or DMN

Methods
37 TBI patients (11 females, age= 42.84) and 16 healthy controls (6 females, age = 38.19) underwent fMRI while viewing abstract images that subjects were asked to remember. Encoding was tested outside the scanner. A median split of performance (d-prime) divided patients into High (HP) and Low Performance (LP) TBI groups. fMRI data were processed using FSL (5). General linear modelling was performed with correct and incorrectly encoded trials included as regressors. Higher level contrast included age as a nuisance variable.

Results
The LP TBI group (n=19; age=45.74) showed abnormally low performance (mean=57.30) compared to the healthy control group (mean=72.51; $p<0.01$) with no abnormality in the HP TBI (n=18;age=45.74) group (Fig. 1a). Successful encoding was associated with extensive activation within the DAN, as well as expected activation in the ventral visual stream and medial temporal lobes. Reduction of activation was seen in the DMN (Figure 1c). For successful encoding the contrast of HP TBI > LP TBI showed increased activation in the left DAN (parietal lobe) as well as left anterior insula and bilateral medial temporal lobes (Figure 1c).

Conclusions
Patients with memory encoding deficits after TBI show reduced activation within the DAN and medial temporal lobes, suggesting that chronic memory impairment after TBI may be associated with a failure of the attentional control of memory encoding.

References
1. Arenth et al., 2012 - J Clin Exp Neuropsychol
2. Kim 2015 - Hippocampus
3. Sharp DJ et al., 2014 - Nat Rev Neurol
4. Han K et al., 2016 - J Int Neuropsychol Soc
5. Smith et al., 2004 – Neuroimage.



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Poster number: P-T130
Theme: Learning & memory

Temporal dynamics of serotonin release in response to discrete gregarising stimuli in the Desert Locust

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Serotonin is involved in the rapid (within hours) and reversible transformation of the Desert Locust (Schistocerca gregaria) between two different phenotypes (phases) - a process dependent on population density. At low density, locusts develop into their solitarious phase, which are slow moving, mainly night active and repelled by conspecifics. With increased density, however, locusts develop into their gregarious phase which are more active and are attracted to other locusts. Gregarisation is mediated through the repeated mechanical stimulation of the hind leg which has been shown to transiently increase serotonin in key neurons of the thoracic ganglia. However, the specific role of serotonin in regulating phase state is yet to be elucidated. We used in vivo fast scan cyclic voltammetry to measure the release of serotonin in the metathoracic ganglia following discrete mechanosensory stimulation. To mimic mechanosensory stimulation from crowded locusts, brush strokes were used to stimulate the hind leg and other non-gregarising sites. The recording electrode was positioned in the metathoracic ganglia, close to the serotonergic neurons. We used serotonin-specific 'N'-voltage waveform to distinguish the serotonin signal from that of other neuromodulators. The amplitude of the oxidation peak of the voltammogram and its latency from stimulus onset were used as measures of serotonin release. In both solitarious and gregarious animals, hind leg stimulation caused a rapid large amplitude release of serotonin due to direct mechanosensory input. By comparison stimulation of the antennae elicited a delayed release of serotonin due to possible indirect descending inputs. Whilst a transient increase in metathoracic serotonin has previously been shown to initiate phase change, our data shows that serotonergic release may also remain involved in the transient responses of gregarious locusts to further gregarising stimuli. This methodology provides novel insight into the rapid dynamics of serotonin release thought to be key in transforming locusts into their swarming state.

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Poster number: P-T131
Theme: Learning & memory

The influence of mammillothalamic tract lesions on hippocampal and retrosplenial cortex function

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The medial mammillary bodies and its projections to the anterior thalamic nuclei via the mammillothalamic tract (MTT) are needed for normal hippocampal and retrosplenial cortex function. MTT lesions produce 'covert pathology' in these distal regions as evidenced by a reduction in markers of neural activity (e.g. the immediate early gene, c-fos). However, it is not known whether these functional changes are accompanied by, or even the result of, structural changes at the dendritic level. To address this, the current study examined dendritic arbor complexity in CA1, dentate gyrus, and retrosplenial granular b cortex (Rgb) and spine density in CA1 and Rgb after bilateral MTT lesions. Rats with MTT lesions (n=9) and sham operated controls (n=11) were tested on a reinforced T-maze alternation task to confirm the efficacy of the lesions. Subsequently, the brains were removed, treated with Golgi-cox stain, and blinded Sholl analysis and spine density counts of three-dimensional image stacks were performed on dendritic arbors. Rats with MTT lesions were impaired on the T-maze task, thus confirming the success of the lesion. Spine density counts showed the MTT lesions significantly reduced CA1 spine density but did not influence the number of intersections in CA1, dentate gyrus, or Rgb after Sholl analysis. Work on Rgb spine density is ongoing and will be presented. Continuing work analysing protein levels of the immediate early gene Arc and brain derived neurotrophic factor (pro-BDNF and mature BDNF forms) in the hippocampus and retrosplenial cortex using Western blotting after MTT lesions will also be presented. Our findings suggest that damage to the MTT causes microstructural changes in the hippocampus as shown by reduced spine density in CA1. These findings provide novel evidence of the importance of ascending mammillary body projections for hippocampal integrity and our additional work will expand our understanding of the distal effects of MTT lesions.

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Poster number: P-T132
Theme: Learning & memory

Stimulation of tone fear memory destabilisation

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The reactivation of a previously-learned memory, in addition to enabling expression of that memory, can lead its destabilisation. Memory destabilisation necessitates subsequent reconsolidation of the memory in order to restabilise it and integrate new information. Disruption of the reconsolidation process, therefore, results in experimental amnesia that might be harnessed translationally to diminish traumatic memories. However, the success with which memory reactivation leads to destabilisation is highly variable. Therefore, strategies to enhance memory destabilisation would be beneficial. Here, we explored potential pharmacological adjuncts to memory reactivation in order to stimulate tone fear memory destabilisation under conditions that do not normally lead to reconsolidation. First, we established that post-reactivation systemic administration of the glucocorticoid antagonist mifepristone (30 mg/kg, s.c.), but not the beta-adrenergic antagonist propranolol (10 mg/kg, i.p.) impaired the reconsolidation of a mildly-conditioned fear memory. Mifepristone also impaired the reconsolidation of a strongly-conditioned fear memory, but only when preceded by systemic injection of the nootropic nefiracetam (3 mg/kg, i.p.) 1 hr prior to memory reactivation. Administration of mifepristone or nefiracetam alone had no observable effect on subsequent fear expression. In contrast, systemic injection of the D1 receptor agonist SKF38393 (5 mg/kg, i.p.) immediately prior to memory reactivation had no impact on cued fear memory destabilisation or reconsolidation. It remains to be determined which target(s) of nefiracetam mediate the destabilisation enhancement observed. These targets include L-type calcium channels and cholinergic receptors, both of which have been implicated in memory destabilisation.

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Poster number: P-T133
Theme: Learning & memory

The role of serotonin in behavioural phase transition in the desert locust

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Desert locusts (Schistocerca gregaria) transform between two extreme phenotypes ('phases') depending on population density. Isolation from conspecifics results in a behaviourally cryptic solitarious phase, whereas crowding leads to an active gregarious phase. Behavioural gregarisation can be induced in the laboratory within 2h of crowding, so S. gregaria provides a useful model for analysing mechanisms underlying phenotypic plasticity. Previous studies have reported that the amount of serotonin (5-hydroxytryptamine; 5-HT) in the thoracic ganglia shows a pronounced increase in the first 4h of gregarisation, which correlates with the degree of behavioural gregarisation in this time window. Our attempts to replicate these effects have been unsuccessful, possibly due to using a different strain of locusts. To better determine the role of 5-HT and the importance of strain in phase change, we compared the behavioural and neurochemical characteristics of two locust strains: one reared on site for many generations (Leicester; 'L'), and the other a recent wild-derived strain (Mauritanian; 'M'). Juvenile solitarious locusts of both strains were either crowded with conspecifics for 4h to induce gregarisation or left uncrowded (controls). Each animal's probability of belonging to the gregarious phase (p.greg) was assessed in an established behavioural assay. The locusts were then snap-frozen and 5-HT was quantified in their thoracic ganglia using HPLC. Solitarious M animals had a significantly higher p.greg than solitarious L animals and had 40% more ganglionic 5-HT. There was no correlation between p.greg and ganglionic 5-HT in either strain. Crowding for 4h gregarised both strains by a similar amount but 5-HT levels increased by less than 6%. These results indicate that the L and M strains differ in behaviour and baseline 5-HT levels, but have a comparable propensity to gregarise. Once again we find no link between 5-HT and behavioural phase transition. Our future work will establish efficacious methods for manipulating 5-HT action in the central nervous system to further clarify the role of 5-HT in gregarisation.

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Poster number: P-T134
Theme: Learning & memory

Deconstructing episodic memories to track their reconstruction in EEG time courses

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Episodic memory refers to our ability to store and to recall our personal experiences. These memories build our personal history, binding together specific details about our past: where, how and what happened in our life. Despite the importance of episodic memory, how the brain manages to bring back our memories is still unknown. Current studies in neuroscience focus on detecting the similarities between the brain pattern elicited during the encoding of an event and its subsequent retrieval, understanding episodic memory as a static "snapshot" of past episodes. Despite valuable results made following this point of view, this approach does not capture the reconstructive nature of our memories and the temporal dynamics of those elements that constitute them.

We here present electrophysiological work, in combination with multivariate pattern analysis techniques, to provide a novel perspective onto the temporal dynamics of memory reconstruction processes, decomposing memory's architecture into relevant sub-components and tracking their re-emergence across the time course of retrieval. The paradigm involves electroencephalography (EEG) recording during the learning (encoding) of novel object-context associations, and the subsequent mental reconstruction of these object-context events. The critical aspect of this paradigm is that the episodes were configured on the basis of three predefined dimensions. The learned events shared a perceptual feature (pictures or drawings of objects), a conceptual relationship (the semantic category to which the objects belongs, e.g. fruits), or a contextual aspect (we used two main categories of context, displaying outdoor and indoor pictures). Using representational similarity analysis and machine learning algorithms, this configuration allowed us to detect at which specific moments across the EEG time course an episode's sub-components are reactivated during retrieval, creating a temporal mapping of perceptual, semantic and contextual features during memory reconstruction. Together, our EEG results suggest that perceptual, semantic and contextual information are recovered at distinct time points after the presentation of a reminder.

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Poster number: P-T135
Theme: Learning & memory

Dopamine is released from the locus coeruleus into the dorsal hippocampus

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Dopamine signaling in the hippocampus mediates aspects of attention and arousal. However, the site of dopamine release that drives the selective attention underlying spatial learning and memory has recently come into question. We attempt to address this problem by utilizing optogenetics to selectively stimulate dopamine release in the dorsal hippocampus (dHPC). Our results indicated that the locus coeruleus (LC) provides the main source of dopamine to the dHPC. We utilized HPLC with electrochemical detection and were able to directly measure co-release of norepinephrine and dopamine in the hippocampus following optogenetic LC axon stimulation. We therefore assayed the function of LC catecholamine release in the dHPC during a learning and memory task. Photostimulation of the LC-to-hippocampus catecholamine pathway enhanced performance in a spatial recognition task via the dopamine D1/D5 receptor, but not via the beta-adrenergic receptor. Optical stimulation of LC axons in the dHPC also increased the rate of learning in the Barnes Maze task. These findings indicate that dopamine is co-released from LC neurons and provide a framework for further exploring catecholamine anatomy and function in the hippocampus.

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Poster number: P-T136
Theme: Learning & memory

Redrawing Papez circuit: Collateral hippocampal projections innervate the rat mammillary bodies and retrosplenial cortex

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Papez circuit remains one of the most cited neuroanatomical concepts [1]. In recent decades its importance for memory and memory disorders has become apparent. Classically, it comprises a unidirectional, return loop from the hippocampus to the medial diencephalon and back, via cingulate (retrosplenial) cortices. While many subicular efferents are segregated by their columnar and laminar origin, the hippocampal projections to the mammillary bodies and retrosplenial cortex (areas 29, 30) appear to arise from overlapping subicular regions in both rats and macaque monkeys [2,3,4]. This overlap led us to inject pairs of retrograde tracers (Fast Blue and Cholera Toxin Subunit B) in these two locations in rats and examine the subiculum for neurons labelled by a single tracer or co-labelled by both tracers. We describe a substantial population of subiculum neurons in the rat hippocampus with collateral projections to both granular retrosplenial cortex (area 29) and the mammillary bodies. Additionally, we sought to describe the neurochemical properties of these projections. These findings challenge ideas of subiculum organisation and reverse information flow in Papez circuit.

1. Papez, J.W. Arch. Neurol. Psychiat. 38, 725-743 (1937)
2. Kobayashi, Y. & Amaral, D.G. J. Comp. Neurol. 502, 810-833 (2007)
3. Van Groen, T. & Wyss, J.M. J. Comp. Neurol. 463, 249-263 (2003)
4. Christiansen, K., Dillingham, C.M., Wright, N.F., Saunders, R.S., Vann, S.D. & Aggleton, J.P. Eur. J. Neurosci. 43, 1044-1061 (2016).

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Poster number: P-T137
Theme: Learning & memory

Cholinergic modulation of DG-CA3 feedforward microcircuit dynamics and function

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Dentate gyrus granule cells provide powerful feedforward excitatory drive onto a local circuit of CA3 pyramidal cells and inhibitory interneurons, and is believed to selectively activate subsets of pyramidal cells in the CA3 recurrent network for encoding and recall of memories. Cholinergic receptors provide a key means to modulate this circuit, increasing cellular excitability and altering synaptic release, but the combined action of these changes on information processing between the dentate gyrus and CA3 remains unknown. We recorded evoked monosynaptic EPSCs and disynaptic IPSCs in CA3 pyramidal cells in response to a range of frequencies and stimulation patterns and in the presence and absence of the cholinergic receptor agonist carbachol (5 µM). We found that carbachol strongly reduced IPSC amplitudes but only mildly reduced EPSC amplitudes. The short-term plasticity dynamics of these responses were used to constrain a computational model of mossy fibre driven transmission across a range of stimulation patterns. This model was then used to analyse how a single cell model of CA3 pyramidal cells driven by constant dendritic current is perturbed by excitatory and inhibitory synaptic input. We show how the timing, frequency, and excitatory-inhibitory balance of mossy fibre input influences the activation of CA3 pyramidal by granule cell bursts, and how the presence of acetylcholine is represented in this parameter space. We then used a spiking network model of CA3 to study encoding and recall of neuronal ensembles driven by mossy fibre input. We found that modification of mossy fibre short term plasticity by acetylcholine altered the balance between encoding and recall. This analysis provides insights into how the dynamics of mossy fibre driven activity affect the function of the CA3 network and how this is modulated by cholinergic input.

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Poster number: P-T138
Theme: Learning & memory

Uncovering unknown developmental disorders through mouse modelling

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Although individually rare, together developmental disorders affect 2-3 % of live births and are a major cause of infant mortality and morbidity. Many developmental disorders have a genetic cause, yet only few affected children receive genetic diagnosis. Deciphering Developmental Disorders (DDD) and Windows of Hope (WOH) are large collaborative projects that aim to understand the underlying genetic causes of such uncharacterised developmental disabilities. Modelling these mutations in animal models will provide evidence supporting a causal link between the candidate genes and the previously uncharacterised developmental disorders, shed light on their underpinning neuronal circuitry, and potentially inform treatment. We have chosen to model mutations in six candidate genes, based on their relatively high causative probability and cover a dynamic mutation range found in developmental disorders, include consanguineously inherited recessive mutations (WOH dataset) and de novo dominant mutations (DDD dataset). The mouse models were either generated with CRISPR/Cas9 system or as standard 'knock-out first' alleles.

One of the recent findings from the WOH project are nine patients with a distinct developmental delay syndrome. All the patients have recessive mutations in the KPTN gene, and have macrocephaly and cognitive disability as their main endophenotypes. We have tested the mice in a series of behavioural assays and morphometric analysis, finding mutant mice accurately phenocopy the hyperactivity, cognitive impairment, and macrocephaly phenotypes observed in the human patients. We have then employed the robust cognitive array of tests, adapted from Kptn mouse model, on the five further mouse lines, each with mutations in a candidate DDD gene. Following learning and memory assays, we are currently carrying out morphometric brain analyses and RNA-sequencing of several associated brain regions in all the lines. Taken together, the results will not only aid biological validation of the candidate genes, but also provide a large scale platform for comparison between several previously uncharacterised developmental disorders.

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Poster number: P-T139
Theme: Learning & memory

Hippocampal projections to nucleus reuniens co-localise with cells that project to the mammillary bodies but not the anteromedial thalamic nucleus

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The thalamic nucleus reuniens occupies a central position in the circuit that links frontal cortical regions with the hippocampal formation. In addition, nucleus reuniens contains head direction cells and is involved in memory related behaviour. As such, nucleus reuniens shares hodological and functional similarities with two groups of subcortical nuclei that are both involved in spatial memory, namely the anterior thalamic nuclei and the mammillary bodies. Accordingly, in two set of experiments we tested whether projections to a) the anteromedial thalamic nucleus and b) the mammillary bodies, originate from either separate or identical cell populations as the ones that project to nucleus reuniens. In a number of adult rats, we injected a retrograde tracer in nucleus reuniens in combination with another retrograde tracer in either the anteromedial nucleus or the mammillary bodies. Our initial data show that the dense hippocampal afferents to nucleus reuniens originate predominantly from the ventral subiculum whereas a more moderate projection originates from dorsal/intermediate subicular levels. This contrast with the projection to the anteromedial thalamic nucleus that originates almost exclusively from the dorsal and intermediate portions of the subiculum. Therefore, although a certain overlap between the two cell populations is present at the intermediate portions, the overall projection pattern indicates that there are two separate cell populations. While projections to the mammillary bodies originate densely from both dorsal and ventral subicular portions, a dorso-ventral distinction is present when comparing with the inputs to nucleus reuniens. Whereas the projections that originate from the ventral subiculum clearly co-localize with the cell population that projects to nucleus reuniens, at more dorsal levels a more discrete pattern appears to be present. A quantitative analysis of the proportion of double-labelled cells is presented in order to estimate the degree of collateralization in both ventral and dorsal subicular pathways.

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Poster number: P-T140
Theme: Learning & memory

Lapses during memory consolidation provide opportunities for memories to be replaced

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Memory consolidation is generally conceived as a process whereby new information sequentially moves to successively longer-term stores. In invertebrates and vertebrates, including humans, there are short periods of memory lapses during consolidation. Formerly these have been regarded simply as moments of vulnerability in memory formation. Our recent work on the snail Lymnaea however suggests that they are adaptive, allowing consolidation to be regulated so that acquisition and storage are effectively modified by new information after initial learning.

Previously, we found that one-trial appetitive classical conditioning using sucrose as the unconditioned stimulus (US) and gamma-nonalactone (GNL) as the conditioned stimulus (CS), was accompanied by lapses in memory expression at 30 min and 2 hour after training. A second training paradigm involved the pairing of amyl acetate (AA) as the CS and sucrose as the US. We first trained the animals for GNL + sucrose (Primary training) and then trained with AA + sucrose (secondary training) at either lapse or non-lapse points of the primary memory and tested for the presence of either memory 24 h later (LTM in Lymnaea). We found that when secondary training was performed at a lapse point it replaced the primary memory. However if it was performed at a non-lapse point then the primary memory was retained and the secondary memory was not acquired.

We show that an inability to form two simultaneous memories was not the reason for the acquisition of only one memory. If the secondary training was performed once the primary memory had been allowed to fully consolidate into LTM (24 h) then the animal was successfully able to acquire both memories.

Using intracellular electrophysiology we were show that an in vitro correlate of the memory and the replacement of memories was present in a reduced preparation. This allowed for the interrogation of the activity of interneurons known to be involved in the maintenance of long-term memory in Lymnaea.

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Poster number: P-T141
Theme: Learning & memory

Imaging the encoding and consolidation of spatial memory in mice

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One of the fundamental questions of neuroscience is the identity of the memory engram. Some recent studies demonstrated the reliance of memory on the activation of distinct neuronal ensembles distributed across the brain. At least some ensembles which form engrams can be identified by the expression of immediate-early genes in a context relevant to the memory. The current study investigated the dynamic nature of cortical neuronal ensembles in mice expressing a short-lived form of EGFP under the control of the c-fos gene promoter. The mice were trained on a 4-arm version of the radial-arm maze (RAM) task and c-fos positive cells were imaged via a cranial window positioned above the retrosplenial cortex (RSC). The RSC is thought to be crucial for navigation and certain types of memory. Specifically, it has been proposed the RSC facilitates the translation between allocentric and egocentric viewpoints by utilising environmental landmarks. Moreover, the RSC also processes wider contextual cues and contributes to the formation of episodic memories. We therefore hypothesised that behavioural training would increase c-fos expression in the RSC and that continued training would lead to the formation of a distinct neuronal ensemble specific to the context of training. We have observed an increase in the fluorescent signal following behavioural training across the RSC as well as the emergence of distinct patterns of neuronal activation, showing varying degrees of overlap throughout the course of training.

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Poster number: P-T142
Theme: Learning & memory

Heart beat and hippocampal processing of external stimuli

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Hippocampus is needed for normal episodic memory. Electrophysiological activity of the hippocampus is characterized by oscillatory phenomena such as theta that mostly takes place when the individual is actively attending to the external world. Hippocampal theta-band (3-8 Hz) responses to stimuli seem to predict learning about those stimuli. Specifically, if stimulation is targeted to a certain phase of the hippocampal theta cycle, hippocampal responses are compromised and learning is retarded (Nokia et al., 2015). Interestingly, it is suggested that heart beat correlates with the hippocampal theta rhythm (Komisaruk, 1970). Here, we tested whether the phase of the cardiac cycle affects hippocampal theta-band responses to external stimulation in adult female New Zealand White -rabbits. All procedures were carried out in accordance with the directive 2010/63/EU of the European Parliament. Under anesthesia, monopolar recording electrodes were implanted to the dorsal hippocampus aiming at the hippocampal fissure. Animals were let to recover and then subjected to a single recording session. During this session, an 8-kHz, 200-ms tone was played 300 times at 75 dB. The inter-trial interval varied randomly between 5 and 15 seconds. Oxygen saturation from the earlobe was measured using a pulse oximeter and heart beat derived from the signal offline using Matlab. Hippocampal local-field potentials were recorded and analyzed offline also using Matlab. Data analysis revealed that hippocampal theta-band responses to the tone were most uniform when the tone onset was aligned with a certain phase of the heart beat/cardiac cycle. Further studies are needed to clarify the behavioral relevance of the connection between the cardiac cycle and hippocampal processing of external stimuli.

References:
Komisaruk BR. (1970) Synchrony between limbic system theta activity and rhythmical behavior in rats. J Comp Physiol Psychol, 70(3):482-92.
Nokia MS, Waselius T, Mikkonen JE, Wikgren J, Penttonen M. (2015) Phase matters: responding to and learning about peripheral stimuli depends on hippocampal θ phase at stimulus onset. Learn Mem, 22(6):307-17.

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Poster number: P-T143
Theme: Learning & memory

JAK/STAT signalling underlies leptin-induced LTD at temporoammonic-CA1 synapses in adult hippocampus

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Evidence indicates that the adipocyte-derived hormone leptin regulates excitatory synaptic transmission within the hippocampus as well as regulating satiety (Irving and Harvey, 2014). In the hippocampus, leptin modulates excitatory synaptic transmission in an age-dependent manner at schaffer collateral (SC)-CA1 synapses (Moult and Harvey, 2011). However, leptin also regulates the anatomically distinct temporoammonic (TA) input to CA1 synapses, as leptin induces a novel form of long term potentiation (LTP) at juvenile hippocampal TA-CA1 synapses (Luo et al. 2015). However the effects of leptin on excitatory synaptic transmission at adult hippocampal TA-CA1 synapses is unknown. Here, we used standard extracellular recordings to investigate the effects of leptin on excitatory synaptic transmission in adult male (12-24 week) rats. Addition of leptin (25 nM; 15 min) induced long term depression (LTD) at TA-CA1 synapses (to 76 ± 5% of baseline; n = 4; $P < 0.001$). This effect was NMDA receptor-dependent as 50 µM D-AP5 inhibited leptin-induced LTD (n = 5). Furthermore JAK2/STAT3 signalling was found to underlie this effect as inhibitors of JAK, (AG490; 95 ± 9% of baseline; n = 5; $P > 0.05$) and STAT3, (stattic; 104 ± 5% of baseline; n = 5; $P > 0.05$) blocked leptin-induced LTD. In immunocytochemical studies, under low Mg2+conditions, leptin resulted in a reduction in GluA1 surface expression in hippocampal cultures (to 79 ± 5% of control; n = 3; $P < 0.01$); an effect that was blocked by inhibitors of JAK/STAT signalling. Accumulating evidence suggests that the JAK/STAT pathway is involved in neuroprotection and AD (Chiba et al. 2009) and leptin prevents the detrimental actions of amyloid beta at hippocampal synapses (Doherty et al, 2013). Thus the ability of leptin to regulate excitatory synaptic strength at TA-CA1 synapses has important implications for leptin's role in health and CNS-driven disease.

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Poster number: P-T144
Theme: Learning & memory

Older and wiser? The effect of age and experience on behaviour of the Desert Locust, Schistocerca gregaria

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Desert Locusts switch reversibly between two strikingly different phenotypes: a shy and cryptic solitarious phase and a more brightly coloured gregarious phase. When population density is low, locusts exist as solitarious individuals. When food shortage forces them closer together however, they become gregarised through close contact with conspecifics: they become more active and are attracted to each other. Solitarious locusts are less willing to initiate walking, and walk more slowly and intermittently than gregarious locusts.

We investigated individual differences and the extent of behavioural plasticity within a phase. Does the 'hesitant' behaviour of solitarious locusts represent a response to unfamiliar environments that can be overcome by familiarity? Can these locusts become more active and behave like gregarious locusts without undergoing gregarisation?

Our arena contained a wooden beam with a holding tube on one end and a food source behind a screen on the opposite end. Air was drawn through the arena to carry the food odour towards the locust in the holding tube. Once a week locusts were tested 6 times in a row (10 min runs, 10 min intervals) for 9 weeks. We fitted mixed-effect Cox regression models to analyse the effect of repeated runs, age and phase state on the time taken to cross the beam.

Naïve young solitarious locusts were initially hesitant, taking longer to cross the beam than naïve young gregarious locusts. However, they became less hesitant over the 6 runs, which we interpret as a consequence of familiarisation with the arena. Over the following 8 weeks these solitarious locusts became progressively less hesitant, eventually matching the shorter crossing times of the naïve gregarious locusts. In a separate experiment, naïve old solitarious locusts had similar crossing times in their first exposure to the assay, to those of old familiarised solitarious locusts, and shorter crossing times than those of gregarious locusts.

Solitarious locusts display age-related behavioural plasticity in locomotion which can exceed the phase-related behavioural range. The hesitant behaviour of solitarious locusts can be overridden by age and experience to result in a locomotory phenotype that is no less hesitant than that found in gregarious locusts.

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Poster number: P-T145
Theme: Learning & memory

The temporal dynamics of human memory replay

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When we remember dynamic events from our past (e.g. driving to the beach last summer), we can vividly replay specific events in front of our mental eye in a temporally structured way. It remains however largely unexplored how the brain orchestrates the replay of dynamic memories, and in particular what the mental chronometry of such dynamic replay is. Recent evidence suggests that oscillatory activity in the alpha rhythm plays an important role in the temporal organisation of neural representations and that decreases in power relate to this phenomenon. We therefore set out to clarify the neural temporal dynamics of memory replay and their relation to the alpha frequency.

In one study we used Magnetencephalography (MEG) and participants were asked to associate a word to one of three scenes within a video clip. Later during memory retrieval subjects were asked to tell in which scene they saw the word. Importantly, to answer this question subjects had to mentally replay the video in order to know the temporal position of the word. In a parallel version of this experiment we recorded electrophysiological activity from patients suffering from intractable epilepsy. These patients were undergoing intracranial recordings for diagnostic purposes. Patients were instructed to associate a word with one of two scenes within a video. At retrieval they were also asked in which scene they remembered the word. To help memory performance the same associations were repeated three times.

Crucially in both experiments we presented (and subjects remembered) the same videos several times but associated with different words. This enabled us to use representational similarity analysis (RSA) in order to track the replay of individual scenes. In both experiments we found sustained power decreases in the alpha frequency range to be associated with successful memory. Studying the time course of replay for different scenes provided new indications on how dynamic memories are replayed, how their neural representations unfold over time.

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Poster number: P-T146
Theme: Learning & memory

Perinatal arsenic exposure induces changes in anxiety-related behavior, learning and memory and brain morphology during postnatal development

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The inorganic form of arsenic (iAs) is at the top of the list of toxic substances threatening human health. Mining and use of pesticides and herbicides are the greatest anthropogenic sources of iAs. Several studies revealed that consumption of As from drinking water in concentration that is higher than permissible limit causes mood disorders and behavioral disturbances in experimental animals. However, little is known how arsenic exposure during prenatal development effects brain and behavior in postnatal development. The aim of our study was to investigate the effects of chronic exposure to arsenic on learning and memory processes and brain morphology in rat's offspring. Experimental animals (wistar rats) were divided into four groups (12 animals in each group): Group I and II – P21 rats at the initial day of experiments, got water containing As (NaAsO2) at concentration 35 ppm and 70ppm correspondingly for 3 month, Group III and IV - offspring of P21 rats got arsenic at concentration 35 ppm and 70 ppm

correspondingly before pregnancy, during pregnancy, and three weeks after parturition. Our experiments, revealed that As exposure through drinking during pregnancy causes reduction in fecundity (number of pups per litter) but doesn't effect the body weight. The present results reveal that 35 ppm and 70 ppm Sodium arsenite does not influence locomotor activity and anxiety behavior in young adult rats, but it causes changes in their pups, specifically the locomotion activity was significantly reduced in pups, whose parents were exposed to As treatment. Also we observed that pups of As exposed parents have a tendency to depression and they perform learning and memory tasks more poorly than control ones. The most prominent changes in brain morphology was revealed in hippocampus CA1 area and motor cortex of offsprings' whose parents got As (70 ppm) before and during pregnancy. The number of cells in these areas was reduced by 20% and the amount of vacuolated cell was increased significantly (p=0,03) compared to control. So we can hypothesize that As effect on animal behavior and brain morphology is more dramatic during prenatal and early postnatal development.

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Poster number: P-T147
Theme: Learning & memory

Individual differences in working memory performance in females: an EEG study

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Introduction: Despite the growing interest to the WM in last decades all existing neuroimaging studies have at least one limitation for investigation of individual differences in WM performance. At first, most of WM studies had been using n-back paradigm but this task can't distinguish manipulation and retention functions. Second, usually the studies included only tasks with moderate difficulty. And last, sample size in the studies didn't exceed 14 subject in each group. In the current study we used varied complexity of the tasks from average to supercomplex and two types of tasks: with mental manipulations and just retention tasks. The main aim of this study was to reveal EEG correlates of individual differences in working memory performance.

Methods: The final sample included 65 women (mean age = 20,92, SD = 2,96). The random sequences of letters of the alphabet were used as stimuli for WM task. Participants were instructed to memorize sets of 5 and 7 letters either without any manipulations (retention task) or after mental recombination of letters in the alphabetic order (manipulation task). EEG data were collected from 19 sites according to standard 10-20 system. All participants were subdivided into two groups separated by the median of their mean performance across the tasks. The groups are referred to as high performance (HP; N = 32) and low performance (LP; N = 33) groups. Segments of raw EEG recorded during the delay period and the resting state EEG were analyzed.

Results and discussion: Our results suggest that the underlying individual differences can be explained by contribution of several factors including (i) a higher level of readiness to process relevant and to inhibit irrelevant information (higher resting alpha in HP group); (ii) stronger engagement of the left prefrontal cortex and the hippocampus; this factor can underlie efficient maintaining and manipulating information in WM due to a fast exchange of information between long term and working memory (higher theta power in the left hemisphere in HP group in the manipulation conditions) and (iii) an energy efficient strategy for distribution of frontal resources in order to maintain the necessary level of activity of the cingulate cortex (higher midline frontal theta power in HP group).

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Poster number: P-T148
Theme: Genetics & epigenetics

Dysregulation of ultradian corticosterone alters glucocorticoid receptor activity and transcription of metabolic target genes in rat liver

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Adrenal ultradian glucocorticoid (GC) secretion is highly conserved within mammals. The GC corticosterone (CORT) is a ligand for the glucocorticoid receptor (GR), inducing GR recruitment to glucocorticoid responsive elements (GREs) to modulate target gene

transcription. Ultradian CORT exposure has been shown to induce pulsatile GR recruitment and transcription of the Period1 gene in brain and liver of adrenalectomized (ADX) rats. In cell lines, constant GC treatment has been further found to induce prolonged GR activity and overexpression of target genes. However, the effect of disrupting the physiological GC pattern in vivo is less well understood.

The liver is a major GC target tissue, and metabolic dysregulation is commonly reported with conditions of GC excess (Cushing's disease), synthetic GC treatment (Cushing's syndrome), and a variety of GC rhythm altering conditions including chronic stress and shift work. Here, we have assessed the direct GR dependent effects on transcription of liver genes during physiological (pulsatile) and non-physiological (constant) CORT replacement in ADX rats. The principle methodology used is ChIP-Seq, next generation genome-wide sequencing of DNA fragments bound by GR or RNA Polymerase (Pol2). Liver samples were collected at 2h20m and 3h (corresponding to pulse peak and nadir respectively) from ADX male Sprague Dawley rats infused with pulsatile or matched dose constant CORT infusion.

GR binding at a large range of genomic sites were found to accurately track the pulsatile peak and trough, whereas constant CORT generally induced sustained GR recruitment. Interestingly, Pol2 activity was found to be highly dynamic and differentially regulated in a pattern-dependent and gene-specific manner throughout GC-regulated gene boundaries. From the dataset so far, we have identified a number of metabolic targets characterised as factors involved in metabolic syndrome pathology (i.e. Lpin1, Sds, Angplt4) that are distinctly and differentiated regulated with the different infusion patterns.

Therefore, we have demonstrated that disrupting the ultradian GC rhythm causes complex genome-wide dysregulation of metabolic targets, potentially playing a direct and causal role in the development of adverse metabolic phenotypes.

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Poster number: P-T149
Theme: Genetics & epigenetics

The role of a long non-coding NOS1-related Natural Antisense Transcript in the regulation of Nitric Oxide signalling

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Nitric oxide (NO) is an important signalling molecule, produced by Nitric Oxide Synthase (NOS) and involved in many physiological functions, including memory formation (Wang, et al. 2016; Korneev et al., 2005) and regulation of neurogenesis (Gibbs, 2003). Through the process of S-nitrosylation, NO can perform post-translational modifications of proteins that are important for their functioning. However, when overexpressed, NO can become toxic to the cell and subsequently contribute to numerous pathologies, such as Alzheimer's disease or cancer (Calabrese, 2007). Therefore, its production must be tightly regulated to maintain the balance between its positive and negative effects.

The production of NO within the brain can be controlled via the regulation of NOS gene expression, and particularly, by non-coding Natural Antisense Transcripts (NATs). In mammals, the NAT for Nos1 (Mm-antiNos1) had been discovered very recently at Sussex Neuroscience Centre. The study by Korneev et al. (2015) revealed that Mm-antiNos1 is dynamically regulated during development. Real time RT-PCR results had shown that the concentration of Mm-antiNos1 is high within the brain during embryogenesis and early postnatal period, but it drops dramatically after mouse reaching 4 months old (see Figure 1). The fact that the concentration of this transcript remains relatively high at site of adult neurogenesis (the olfactory bulb) throughout the adulthood strongly suggests that Mm-antiNos1 may be involved in positive regulation of NO-dependent neurogenesis in mammals.

In the current experiment, we are extending these studies by addressing the cellular localisation of both Nos1 and Mm-antiNos1 transcripts within the brain. By using in-situ hybridisation technique we investigate the cellular and regional distribution of these transcripts at different developmental stages. The experiment contributes to the better understanding of the Mm-antiNos1 RNA functional role in NO regulation and possible contribution to mammalian neurogenesis.

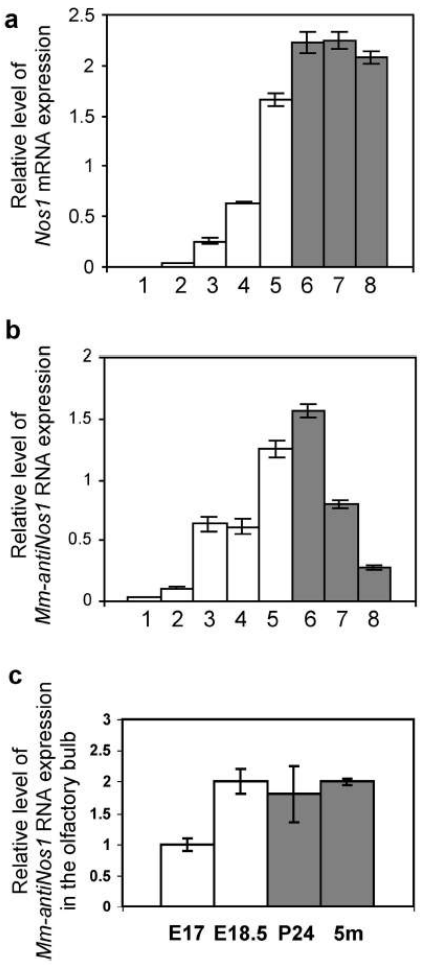

Figure 1. The results of real-time RT-PCR analysis of the expression of *Nos1* mRNA (**a**), and *Mm-antiNos1* transcript (**b**) in the mouse brain at different developmental stages (in days): 1 – 9.5, 2- 11.5, 3 – 13.5, 4 – 15.5, 5 – 18.5, 6 – P1, 7 – P20, 8 – 4 months. **c:** The expression of *Mm-antiNos1* in the olfactory bulb at days 17 and 18,5 of embryonic development (white bars), 24 days postnatally and over 5 months old (grey bars). From Korneev et al., 2015.

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Poster number: P-T151
Theme: Genetics & epigenetics

The role of the blood-brain barrier tight junction protein claudin-5 in behaviour

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There is increasing evidence to suggest that variations in the claudin-5 gene may be linked to schizophrenia; in particular the prevalence of psychosis in 22q11 deletion syndrome where individuals are also haploinsufficient for claudin-5. However, understanding the role of claudin-5 in terms of behaviour has been difficult due to the lethality of knocking out the gene in mice and the lack of tools to suppress claudin-5 expression in vivo. Using RNA interference, we have generated two models that allow us to suppress claudin-5 expression in vivo: 1) An inducible knock-down mouse model to globally suppress claudin-5 expression across the mouse brain; 2) An adeno-associated virus (AAV) to suppress claudin-5 expression in specific brain regions. This has allowed us to investigate the effect of increasing blood-brain barrier permeability on behaviour in the mouse. For AAV injections, we targeted

the dorsal hippocampus (Hipp) and the medial prefrontal cortex (mPFC). All mice were ran on a behavioural test battery covering learning and memory, affect, social behaviour, locomotor activity, and sensorimotor gating. We found that global suppression of claudin-5 was associated with significant impairments in recognition and spatial memory, significant increases in anxiety, and significantly impaired sensorimotor gating. In the mPFC, claudin-5 suppression significantly impaired recognition and spatial memory, and enhanced performance in the forced swim test. In the Hipp, claudin-5 suppression significantly impaired grooming behaviour, and performance in the social preference task. Global suppression of claudin-5 over a sustained period (3 weeks or more) resulted in spontaneous and marked shifts in behaviour. These animals showed seizure-like activity (behavioural arrest; hyperlocomotion; tail flicking) before becoming inactive and dying (approximately 48 hours following onset of symptoms). This is the first evidence to show that direct modulation of blood-brain barrier permeability (both across the brain and in specific regions) is associated with changes in mouse behaviour that are similar to those seen in human psychosis. Interestingly, long-term suppression of claudin-5 causes a profound change in cerebral physiology and behaviour that may be epileptic in nature.

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Poster number: P-T152
Theme: Genetics & epigenetics

Investigating the neural mechanisms that underlie neurodevelopmental disorders associated with EHMT1

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Euchromatic Histone Methyltransferase 1 (EHMT1) encodes a protein involved in transcriptional repression through the addition of mono/dimethyl groups at lysine-9-histone 3 and complete loss (haploinsufficiency) or functional mutations in one of the copies of this gene have been implicated in neurodevelopmental disorders including Kleefstra Syndrome, autism and schizophrenia. In the mouse, Ehmt1 is highly expressed throughout the brain during embryonic development, with much lower levels and more restricted expression in the adult brain. Work in our lab showed that Ehmt1+/- mouse embryonic stem cells (ESCs) could be differentiated into biochemically normal neural progenitor cells but in significantly reduced numbers. These findings indicate an important role for Ehmt1 during brain development and suggesting a neurogenic component to its function. Here we aim to explore the neurogenic role of Ehmt1 in the brain further, using both a cellular and animal model approach.

We have established a novel conditional heterozygous knockout Ehmt1 mouse line by crossing a floxed Ehmt1 mouse line with a D6-Cre mouse line leading to forebrain specific deletion mouse model (Ehmt1D6cre/+). To discern whether haploinsufficiency of Ehmt1 leads to altered neurogenesis using BrdU on sectioned brain samples from adult Ehmt1D6cre/+ knockouts and Ehmt1flx/+ littermate controls. Initial data suggest no difference in proliferation between adult Ehmt1D6cre/+ and Ehmt1flx/+ littermate controls. We are now going on to assess survival and differentiation rates differences in these mice. Additionally, these ex vivo data will be complemented by analysis of primary cell cultures derived from Ehmt1D6cre/+ brain. Finally, the functional consequence of Ehmt1 haploinsufficiency in the brain has been assessed using behavioural tasks of relevance to the associated neurodevelopmental disorders and/or linked to neurogenesis. We demonstrate that Ehmt1D6cre/+ knockouts have deficits in sensorimotor gating using the acoustic startle task, and impaired learning and memory using the novel object recognition task and 1-choice serial reaction time task. Taken together, these data provide insight into the neural mechanism that underlie the neurodevelopmental disorders associated with EHMT1 mutation.

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Poster number: P-T153
Theme: Genetics & epigenetics

The effects of a low-protein maternal diet on offspring behaviour: a causal role for Cdkn1c?

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Adverse in utero factors, including an insufficient maternal diet, are associated with an increased risk of neuropsychiatric disorders in offspring. Imprinted genes, which are monoallelically expressed (i.e., from one parental allele) due to epigenetic regulation, are sensitive to the prenatal environment. Consequently, changes in imprinted gene expression may mediate the effects of maternal

diet on postnatal neurobehavioural outcomes. Cdkn1c, a maternally expressed gene involved in midbrain dopaminergic neuron differentiation, has been implicated in the effects of a prenatal low-protein diet (LPD) on offspring brain and behaviour. Work from our lab suggests that this gestational LPD results in biallelic Cdkn1c expression and that overexpressing Cdkn1c elicits a similar phenotype to mice exposed to a prenatal LPD. Here, we investigated whether reducing Cdkn1c using a paternally-inherited knockout (KO) rescues the effects of a prenatal LPD on offspring behaviour. Adult offspring of mouse dams fed either a basal diet or LPD during gestation completed a series of behavioural tasks assessing locomotor activity (over four days), prepulse inhibition (PPI), anxiety, social behaviour, and reward-sensitivity. A prenatal LPD was associated with a slower rate of habituation to a novel environment, indicated by increased activity levels on day two. However, this effect was not normalised by reduced Ckdn1c dosage. There were no significant effects of prenatal diet or genotype on PPI or anxiety. Unexpectedly, in the basal diet condition, KO mice won more encounters than wild types in the tube dominance test (although this did not reach statistical significance) and made fewer ultrasonic vocalisations to a female in oestrus. In addition, KO mice consumed less of a palatable solution without a reduction in lick cluster size, suggesting altered satiety despite an intact hedonic response. Although the role of Cdkn1c in mediating the effects of maternal diet are not clear from these findings, they provide further evidence that Cdkn1c plays a role in regulating social behaviour and responses to rewarding stimuli. Furthermore, these data suggest that the paternal allele of Cdkn1c may normally be active at some stage of brain development and have a lasting influence on behaviour.

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Poster number: P-T154
Theme: Genetics & epigenetics

Vitamin intake and methyltransferase variant associated with change in visuospatial associative memory performance

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Epigenetic modifications and their mechanisms are under increasing scrutiny in research of health and disease states. Such processes are implicated as biological mechanisms of interaction between genetics and environmental influences such as dietary intake, physical exercise, and psychological stressors. One such modification, DNA methylation, has been associated with risk for familial forms of dementia, developmental delay syndromes, and disparate cognitive phenotypes. We hypothesise that genetic variation within methylation protein genes underlies change across multiple methylation states and consequently may influence cognitive function and disease status.

Using data from the OPTIMA study for individuals with mild cognitive impairment and the TwinsUK study of health in the general population, we investigated the effect of genetic variation within a DNA methyltransferase gene, DNMT3L, on cognitive performance. By analysing domains of cognition sensitive to dementia progression, we report a previously unseen relationship between B vitamins, homocysteine levels, and a functional variant within DNMT3L with cognitive decline and rates of brain atrophy.

To confirm the functional impact of this DNMT3L variant on normal DNA methylation behaviour, we applied in silico modelling analysis to investigate structural, thermodynamic, and electrostatic changes to the protein. The in silico analyses indicated that this variant causes disruption to the interaction sites between DNMT3A and DNMT3L, a complex necessary for normal methylation. By influencing this complex and the interaction with histone H3, the DNMT3L functional variant is likely to trigger genome-wide changes in methylation patterns. These findings provide a mechanistic understanding of genotype-epigenome-environment interactions which contribute to cognitive decline. Targeting key elements of these pathways at the early stages of cognitive disease could provide a viable treatment option for those at risk of dementia.

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Poster number: P-T155
Theme: Developmental neuroscience

Developmental profiling of striatal medium-size spiny neurons

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Medium-size spiny neurons (MSNs) are the major population of neurons in the striatum. All MSNs are born from neural progenitors in the lateral ganglionic eminence before migrating to the striatum. Normal striatal function depends on the accurate development of the electrical and morphological properties of the MSNs and their reciprocal connectivity. How these properties are established early in development and to what extent these emerge in parallel in the two main MSN types; the DrD1- and DrD2-expressing MSNs, is currently unknown. This is important to understand if we are to investigate the striatal circuitry in a range of basal ganglia developmental disorders.

We set out to characterize the development of the electrical and morphological properties as well as their reciprocal connectivity of DrD1 and DrD2 striatal MSNs at postnatal day 3-6, postnatal day 9-12 and at postnatal day 28 and older. We performed whole-cell patch-clamp recordings of MSNs in acute striatal slices of mice combined with posthoc immunocytochemistry to classify MSN type. We find that the electrical properties similarly develop for the DrD1 and DrD2 MSNs, including a gradual decrease in input resistance, an increase in firing rate and a more hyperpolarized resting membrane potential. DrD2 MSNs exhibit an increased excitability in all ages investigated. Conversely, the morphological properties of both types of MSN also develop in parallel, including an increase in dendritic length and complexity and a gradual change from a reticular to radial dendritic arborisation. Reciprocal synaptic connectivity seems to emerge at relatively late stages of development. In conclusion, our results suggest that the developmental time-course of both the electrical and morphological properties is similar for both the DrD1 and DrD2 population of MSNs.

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Poster number: P-T156
Theme: Developmental neuroscience

Experience-dependent developmental changes in astrocyte and synapse distribution in the mouse barrel cortex

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Astrocytes provide structural and biochemical support for neurons and they are involved in synaptic plasticity. They are proposed to play a role in the changes to neuronal and synaptic structure and function during postnatal development. To investigate this, we monitored changes in astrocyte and PSD95 (a major postsynaptic protein) distribution during the neonatal development of the mouse cortex. Labelling astrocytes with SR101, we studied the developmental profiles of astrocyte distribution in the barrel cortex using 2-photon imaging of mouse pup thalamocortical slices. Astrocyte localisation patterns were measured in the first 3 postnatal weeks, when synaptogenesis is highest. Astrocyte density decreased during development and the cells preferentially distributed within the barrel structures during the major period of synaptogenesis, but afterwards they became more equally dispersed across the tissue. This strategic astrocyte positioning suggests an involvement in synaptic development in this area. Since whisker experience influences the synaptic and circuit development of the barrel cortex, we investigated a possible astrocyte effect during experience-dependent plasticity. Following daily one-sided whisker trimming of pups, we compared astrocyte densities with sham-trimmed, age-matched animals. Surprisingly, we did not find any difference between the two groups, suggesting that synaptic changes following sensory deprivation do not affect astrocyte distribution. PSD95 is the major postsynaptic density protein in glutamatergic synapses and its synaptic localisation correlates with synaptic plasticity. However, its developmental spatiotemporal distribution is unknown. We used a PSD95-eGFP knock-in mouse line and observed that most PSD95 was found in small fluorescent puncta. As synapses formed and matured, we measured an increase in the density of the puncta. The investigation of layer-specific distribution of PSD95 revealed an age-specific expression pattern. PSD95 clusters were first strongly detected within the barrels in layer 4, in layer 1 and layer 5A; this was followed by a later increase in layer 2/3. These changes in relative levels of fluorescence may mirror the spatiotemporal sequence of the formation of synapses during development in this area.

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Poster number: P-T157
Theme: Developmental neuroscience

Effects of neonicotinoids on the behaviour and development of the model nematode C. elegans

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Neonicotinoids are currently the most widely used insecticides in the world. Although non-toxic to mammals, they have been found to harm other organisms. The list of impacted species includes both non-target insects such as bees as well as other invertebrates e.g., snails. Linked by the food chain, neonicotinoids are also harmful to vertebrates such as insectivorous birds.

Our study aims to determine the effects of neonicotinoids on the model invertebrate, Caenorhabditis elegans (C. elegans), which is not an intended target for the neonicotinoids. C. elegans was exposed acutely and chronically to clothianidin, nitenpyram and thiacloprid in the high µM to low mM concentration range. The results showed modest to no effect to C. elegans' locomotion, feeding, egg-laying and egg-hatching. This is largely due to the worm's cuticle that acts as a protective barrier. Repeating the experiment with a C. elegans' mutant with a cuticle that is more drug permeable, revealed the efficacy of the test neonicotinoids. In addition, exposure of developing wild-type worms to the neonicotinoids found that while thiacloprid delayed their development, the same concentration of clothianidin or nitenpyram did not. Preliminary data suggest that this is accompanied by significant morphological changes, including alteration of the reproductive system. Similar results have been observed in neonicotinoid-exposed developing queen bees (Williams et al., 2015).

In this study we found that relatively high concentrations of neonicotinoids do not have an effect on C. elegans. Exploring this further, our results highlight the importance of the cuticle in forming a protective barrier for the nematode. However, there is a distinction between the neonicotinoids studied as thiacloprid delays neurodevelopment. Future research is aimed at determining the molecular targets responsible for these neonicotinoid-induced developmental defects. Using C. elegans as a model system, we also wish to establish if there is a common mechanism in bees. This will further our understanding of the molecular basis of neonicotinoid toxicity for non-target species.

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Poster number: P-T158
Theme: Developmental neuroscience

Embryonic and postnatal neurogenesis produce functionally distinct subclasses of dopaminergic neuron

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Most neurogenesis in the mammalian brain is completed embryonically. In certain areas, however, the constitutive production of neurons continues throughout postnatal life, producing new cells that contribute distinct functions within existing circuits. These include dopaminergic (DA) cells in the olfactory bulb (OB), local interneurons that play a key role in the earliest stages of sensory processing. The functional properties of adult-generated OB DA neurons have been assumed to match those of their embryonically-produced counterparts. However, we show here that embryonic and adult neurogenesis produce separate DA populations with distinct structural and functional features. We identify two distinct subclasses of OB DA neuron, defined by the presence or absence of a key subcellular specialization: the axon initial segment (AIS). Morphologically, AIS-positive DA neurons have a large soma, an extended dendritic tree, and an axon that contacts multiple glomeruli. AIS-negative DA neurons, on the other hand, are small, anaxonic cells whose exclusively dendritic processes ramify across very few glomeruli. Ontologically, AIS-positive DA neurons are only produced during early embryonic stages and then persist throughout life, leaving AIS-negative cells as the only DA subtype to be continually generated via adult neurogenesis. Crucially, we find that these two modes of production also produce functionally distinct DA populations: large DA cells are more intrinsically excitable, and display stronger and more broadly-tuned responses to odorant stimuli in vivo. Embryonic and postnatal neurogenesis therefore generate DA cohorts that differ both morphologically and physiologically, placing important constraints on the potential functional roles of adult-born neurons in sensory processing.

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Poster number: P-T159
Theme: Developmental neuroscience

The impact of early life stress on young adults' visual ERP responses to facial emotional expressions

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Early life stress (ELS), such as abuse or neglect, is associated with increased rates of mental illness in adulthood. The mechanisms underlying this relationship are unclear, but one theory suggests that ELS gives rise to adaptations in neural processes which subsequently increase the individual's vulnerability to mental illness. These adaptations, such as enhanced identification of anger in facial expressions, are beneficial in abusive childhood environments, but become maladaptive when applied to healthy relationships later in life. EEG studies have shown that children with high levels of ELS show alterations in face-sensitive event-related potentials (ERPs), including early visual waveforms such as childhood and infant precursors to the N170. However, it remains unclear whether this disrupted neural responding to emotional facial expressions is also present in adults who experienced ELS. We therefore used EEG to investigate neural responses to angry, happy and neutral male and female facial expressions in 61 women aged 18 to 25 (mean age 19.8 years), none of whom had been diagnosed with a mental illness, who reported high or low rates of ELS. This age range represents a crucial stage in development, when final brain maturation processes are still taking place. It is therefore vital to identify any ELS-related alterations in processing which could leave these individuals vulnerable to the development of mental illness. Preliminary analyses of the data show differences between the individuals with high and low ELS. These differences are localised to the right hemisphere and show altered N170 responses to angry female faces relative to other facial expressions. These data suggest that ELS-related disruptions in neural responses to facial emotions are a legacy phenotype of early life experiences, which could be a signature of latent vulnerability in individuals who have experienced ELS. Whether this altered neural signature represents a risk factor for future mental illness, or a sign of adaptive resilience in these individuals, warrants further investigation.

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Poster number: P-T160
Theme: Developmental neuroscience

Maternal protein restriction around conception is associated with offspring adult short-term and long-term memory deficits

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Maternal malnutrition during pregnancy is detrimental to foetal development and increases the risk of many chronic diseases in later life i.e. neurological consequences such as an increased risk of schizophrenia. Previous studies have shown maternal protein malnutrition during pregnancy and lactation compromises brain development in late gestation and after birth, affecting structural, biochemical and pathway dynamics with lasting consequences for cognitive function. However, the importance of nutrition during early pregnancy for brain development is unknown. We have previously shown maternal low protein diet confined to the preimplantation period (Emb-LPD) in mice is sufficient to induce cardiometabolic in adult offspring. We have also shown in the foetal brain that Emb-LPD and sustained LPD reduce neural stem cell & progenitor cell numbers through suppressed proliferation rates in both ganglionic eminences & cortex of the foetal brain at E12.5, E14.5 & E17.5 ($p<0.01$). Moreover, Emb-LPD causes remaining NSCs to upregulate the neuronal differentiation rate in compensation beyond control levels during gestation. Therefore, we investigated if there were changes in the adult offspring brain morphology & memory.

Using a diet model, female mice were fed different diets from conception to the end of pregnancy: normal protein diet (NPD), low protein diet (LPD) or embryonic LPD (Emb-LPD: LPD for 3.5 days, NPD thereafter). We carried out a number of behavioural tests at multiple age in the adult offspring, including the short-term memory novel object recognition and long-term memory test T- maze. We have also carried out western-blot for neuron (NeuN) and astrocyte markers (GFAP) on the cortex of the offspring brains.

The Emb-LPD adult offsprings show a highly significant deficit in the short-term memory test in both males and females (figure 1; $p<0.001$). These animals also have a long-term memory deficit, present in both genders & in LPD males ($p<0.01$). Moreover, we have seen an increase in astrocyte marker ($p<0.05$) but no change in neuron marker in the Emb-LPD group cortex.

These data are the first to demonstrate clearly that poor maternal nutrition around conception is associated with adult offspring memory deficits and possibly an increase in astrocytes.

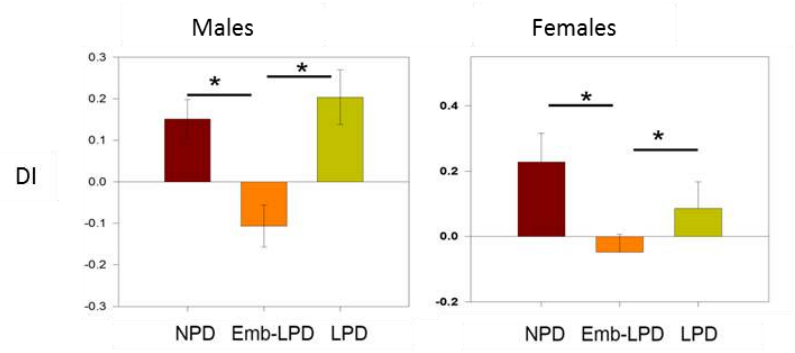

Figure 1. Novel object recognition test analysis. The 'Discrimination Index' (DI). Novel object is assessed between the adult offspring at postnatal day 64 in the three diet groups NPD, Emb-LPD & LPD. *p=0.00001, analysis in 10 males and 10 females from 11different mothers per group.

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Poster number: P-T161
Theme: Developmental neuroscience

Social influence on prosocial behaviour across the lifespan

Authors: Lucy Foulkes, Jovita Leung, Lisa Knoll, Sarah-Jayne Blakemore - *Institute of Cognitive Neuroscience UCL*

Social influence refers to the phenomenon by which an individual's thoughts or behaviours are affected by those of other people. There are significant age effects on social influence, with previous research showing either a decline from childhood to adulthood, or a temporary increase in social influence during early adolescence. To date, most research has focussed on negative aspects of social influence, such as peer influence on risky behaviour. The current study investigated the impact of social influence on the reporting of prosocial behaviours, such as helping others. Participants (N=787) aged 8 to 79 completed a computerised task in which each trial was made up of three components. First, the participant rated how likely they would be to engage in a prosocial behaviour, e.g. 'Looking after an ill friend' (rating 1). Second, participants were shown the average rating (in fact fictitious) that other participants had answered to the same question (provided rating). Finally, participants were asked to rate their own answer again to the same question (rating 2). We found that age affected the extent to which participants were influenced by other people's ratings (i.e. age affected how much participants changed their answer from rating 1 to rating 2). The study provides evidence that social influence is a significant factor in prosocial as well as antisocial behaviours, and that younger people's increased susceptibility to social influence can have positive outcomes.

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Poster number: P-T162
Theme: Developmental neuroscience

Unexpected mesencephalic origin of local inhibitory interneurons in the thalamus

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GABAergic interneurons are a fundamental structural and functional component of all complex neural circuits. Within the thalamus there are two main sources of inhibition, the thalamic reticular nucleus (RTN) and local interneurons, and little is known about the origin and diversity of the latter. In rodents, thalamic local interneurons are largely restricted to the dorsal lateral geniculate nucleus (dLGN), where they contribute to the processing of visual information. Here we examine the ontogeny and function of this local inhibitory drive.

The prosomeric models posits that all thalamic neurons are specified within the second (also known as dorsal thalamus) and third (also known as ventral thalamus or prethalamus) diencephalic prosomeres (p2 and p3). Inhibitory neurogenesis, including that of the RTN, takes place in p3 and in a GABAergic rostral p2 subdomain (pTh-R), which makes both p3 and pTh-R possible sources of origin for thalamic local interneurons. In fact, until now, the prevailing hypothesis states that dLGN interneurons have a prethalamic origin (p3).

In contrast, here we report that p3 or pTh-R are unlikely sources for thalamic interneurons. Using fate-mapping, time lapse imaging and transcription factor expression analysis, we show that Sox14/Gata2/Otx2-expressing precursor cells populate the dLGN with GABAergic interneurons, migrating from the dorsal midbrain in early postnatal development. This unexpected extra-thalamic origin differentiates them from the thalamic GABAergic neurons of the RTN.

The developmentally-defined genetic identity of the dLGN interneurons was then used to perform a combination of optogenetic and electrophysiological experiments. We were able to demonstrate that this cell type can generate tonic inhibition onto thalamic relay neurons, which becomes significant at high interneuron firing rates.

In conclusion, by revising the model of thalamic interneuron ontogeny, we demonstrate how a previously unappreciated mesencephalic inhibitory population controls thalamic relay neuron excitability.

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Poster number: P-T163
Theme: Psychiatry & mental health

Coherence of Personality pattern with depression; where axis I meets axes II

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We carried out intensive research on understanding of the underline neurobiological mechanism of stress induced depression on the brain hardware; however, it seems that the main picture located behind the cognition; where the software meets the hardware. As one line of our projects the present study aimed to evaluate the coherence of Personality pattern with depression.

Volunteer individual with diagnoses of depression were referred to our laboratory randomly (n=12). Beck Depression Inventory (BDI),Millon clinical Multiaxial Inventory-II(MCMI-II), were used at per-test, post-test, and follow up. The results were analyzed, using SPSS statistical package.

The results showed that there was a significant correlation between personality pattern and the intensity of depression. After the application of CBT procedures and the improvement of depression also reduced the personality patterns of schizoid by D=13.75 +/- 3.42 (F=15.42), Avoidant by D=27.25+/-7.82 (F=24.66), Dependent by D=22.63 +/- 9.89 (F=5/23), Passive aggressive by D=14.5 +/- 5.57 (F=6.76), and self defeating by D=21 +/-7.8 (F=6.36)

These finding suggest coherence of personality pattern as axes II with depression as an axes I mental states; and correlation between the hardware and software.

Keywords: Hardware, Software, Personality Pattern, and Depression

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Poster number: P-T164
Theme: Psychiatry & mental health

Dissociable Temporal Effects of Bupropion on Behavioural Measures of Emotional and Reward Processing in Major Depressive Disorder

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Background: Previous research has shown that early in treatment, prior to an improvement in mood, serotonergic and/or noradrenergic antidepressants can remediate negative biases in information processing observed in major depressive disorder

(MDD). However, it remains unclear whether dopaminergic antidepressants, such as bupropion, exert similar early actions on information processing. Here we investigate the early and longer-term effects of bupropion on behavioural measures of emotional and reward processing in MDD patients.

Method: Complete data sets were obtained for 41 MDD patients and 40 healthy controls (HC). In a repeated measures study design, open-label bupropion was administered to just the MDD patients over a 6 week period. All participants completed the Emotional Test Battery and a reward task at baseline, week 2 and week 6.

Results: Bupropion was found to reduce negative biases in emotional processing on the ETB early in treatment at 2 weeks. Specifically, only the bupropion-treated MDD group displayed a significant decrease in the percentage misclassification of faces as sad ($F1, 80 = 4.09$, $p < 0.05$; $t41 = 2.72$, $p < 0.05$) and the number of negative self-referent words falsely recalled ($F1, 81 = 5.73$, $p < 0.05$; $t42 = 2.12$, $p < 0.05$) between baseline and week 2. Conversely, bupropion was found to significantly worsen performance on the reward task between baseline and week 2 ($t14 = 4.17$, $p < 0.01$) prior to normalisation to HC levels after the full 6 week treatment ($t14 = -10.5$, $p < 0.001$; $t28 = -0.25$, $p = 0.80$).

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Poster number: P-T165
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-T166
Theme: Psychiatry & mental health

Psychosis Risk Candidate ZNF804A Localizes to Synapses and Regulates Neurite Formation and Dendritic Spine Structure

Authors: Deepak Srivastava, Michael Deans - *Basic and Clinical Neuroscience Institute of Psychiatry, Psychology and Neuroscience*

Variation in the gene encoding zinc finger binding protein 804A (ZNF804A) is associated with schizophrenia and bipolar disorder. Evidence suggests that ZNF804A is a regulator of gene transcription and is present in nuclear and extranuclear compartments. However, a detailed examination of ZNF804A distribution and its neuronal functions has yet to be performed. Therefore, we examined the localization of ZNF804A in neurons derived from human neural progenitor cells, human induced pluripotent stem cells, or in primary rat cortical neurons. In addition, we used small interfering RNA-mediated knockdown of ZNF804A investigate the role of this protein in neurite formation and structural plasticity of excitatory synapses. We found that ZNF804A protein localized to somatodendritic compartments and colocalized with the putative synaptic markers in young neurons derived from human neural progenitor cells and human induced pluripotent stem cells. In mature rat neurons, Zfp804A, the homolog of ZNF804A, was present in a subset of dendritic spines and colocalized with synaptic proteins in specific nanodomains, as determined by super-resolution microscopy. Interestingly, knockdown of ZNF804A attenuated neurite outgrowth in young neurons, an effect potentially mediated by reduced neuroligin-4 expression. Furthermore, knockdown of ZNF804A in mature neurons resulted in the loss of dendritic spine density and impaired responses to activity-dependent stimulation.These data reveal a novel subcellular distribution for ZNF804A within somatodendritic compartments and a nanoscopic organization at excitatory synapses. Moreover, our results suggest that ZNF804A plays an active role in neurite formation, maintenance of dendritic spines, and activity-dependent structural plasticity.

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Poster number: P-T167
Theme: Psychiatry & mental health

Prognostication of neurocognitive and functional outcomes after traumatic brain injury using the Glasgow Coma Score

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Traumatic brain injury (TBI) is a major cause of morbidity and mortality worldwide. A clear understanding of the relation between acute clinical presentation and chronic neurocognitive and functional deficits is important in order to build better predictive models. The Glasgow Coma Scale (GCS) quantifies the neurological state of TBI patients by assessing verbal, motor and eye-opening responses. TBI patients are often stratified in terms of injury severity using GCS in research, but its prognostic accuracy is debated. We explored the predictive value of GCS in cognitive, physical, social and emotional outcome six months after TBI. TBI patients (n = 138; 40% female; GCS 3–15) aged 17 to 70 years completed a battery of cognitive and questionnaire measures six months after injury. Age and education matched orthopaedic trauma patients (n = 25) and healthy volunteers (n = 99) acted as controls. A clear dichotomy in the functional and cognitive measures that were predicted by GCS was observed, as reflected by the strength GCS correlation and the pattern of group differences. GCS predicted functional outcome in physical and social domains (disability, physical functioning, social functioning) but not in emotional domains (depression, well-being, subjective general health, subjective bodily pain). GCS also predicated outcome in the majority of cognitive domains (verbal fluency, episodic memory, learning, visual and spatial short-term recognition memory, sustained attention) but with the clear exception of working memory (WM; WM span, maintenance and manipulation of information in WM, attentional flexibility). We also observed a strong dissociation in six month outcome between mild and severe TBI cases (according to GCS) in the absence of dissociation between moderate TBI cases and other groups. These findings suggest that the stratification of TBI patients according to GCS for research purposes could be limited to mild and severe (and not moderate) cases. Although GCS may be useful for identifying TBI patients that could benefit from cognitive and occupational rehabilitation, the use of prognostic factors other than GCS are necessary to identify patients requiring early intervention for the prevention of emotional difficulties.

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Poster number: P-T168
Theme: Psychiatry & mental health

Manipulating innate immunity impacts fear reactivity

Authors: Laura Westacott - *Neuroscience and Mental Health Research Institute Cardiff University*, Niels Haan - *Neuroscience and Mental Health Research Institute Cardiff University*, Trevor Humby - *Neuroscience and Mental Health Research Institute Cardiff University,* Timothy Hughes - *Systems Immunity Research Institute Cardiff University,* Paul Morgan - *Systems Immunity Research Institute Cardiff University,* Lawrence Wilkinson - *Neuroscience and Mental Health Research Institute Cardiff University,* William Gray - *Neuroscience and Mental Health Research Institute Cardiff University*

The complement system, a highly conserved branch of innate immunity, is emerging as an important contributor to normal and abnormal brain function. Using genetically modified mice deficient in either the central complement component C3, or the receptor for the C3 bioactive breakdown product C3a, known as C3aR, we investigated fear reactivity using the elevated plus maze and open field assays. Our data demonstrated a markedly heightened anxiety response in C3aR-/- subjects, as evidenced, respectively, by a profound reduction in open arm exploration (see figure) and central zone crossing in the open field (data not shown). This effect was absent from C3-/- subjects. Our data are consistent with a) an important role for C3aR in maintaining normal fear responses and b) the speculation that C3aR signaling is promiscuous and likely to be able to signal via ligands other than C3a. The mechanistic underpinnings of these effects are currently under investigation.

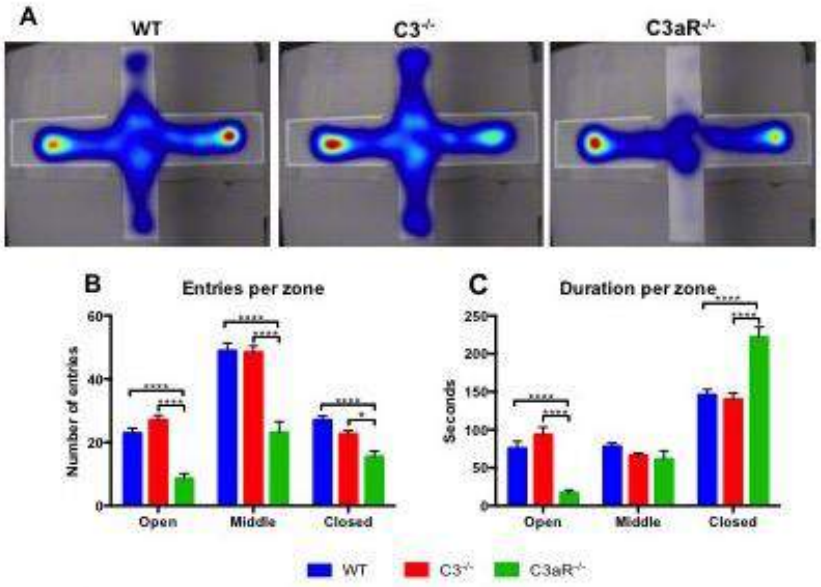

Figure 1. C3aR deficiency is anxiolytic in the elevated plus maze (EPM). A) Merged heat maps depicting exploration of the EPM by wild type (WT), $C3^{-/-}$ and $C3aR^{-/-}$mice. **B)** Mean number of entries to open, middle and closed regions of the EPM. **C)** Average duration spent in middle, open and closed regions. WT N=12, $C3^{-/-}$ N= 12, $C3aR^{-/-}$ N=10. Data represents mean + SEM. *= $p < 0.05$, **= $p < 0.01$, *** = $p < 0.001$, **** = $p < 0.0001$.

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Poster number: P-T169
Theme: Psychiatry & mental health

Reliability and Validity of Turkish Version of the Fear of Happiness Scale

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The purpose of this study was to adapt the English version of Fear of Happiness Scale into Turkish language. Exploratory (N = 171) and confirmatory factor analysis (N = 171) indicated that the Fear of Happiness Scale (FHS) is unidimensional. The results also showed that the Turkish version had good internal consistency (a = .86). In addition, the scale provided acceptable evidence of convergent validity by negatively correlating with measures of positive affect, life satisfaction and subjective happiness and

positively correlating with measure of negative affect. These findings indicated that Turkish version of FHS can be used as a reliable and valid measure in Turkish culture.

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Poster number: P-T170
Theme: Psychiatry & mental health

Glutamatergic dysfunction leads to a hyper-dopaminergic phenotype: a possible cause of aberrant salience

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Current thinking suggests that psychosis is a disorder of aberrant salience. This describes when a stimulus continues to grab inappropriately high levels of attention, and it is thought to be mediated via elevated dopamine (DA) levels, which have been robustly demonstrated in schizophrenia. However, the causes of this DA dysregulation are generally unspecified. Recent large scale GWAS meta-analyses have established genome-wide significant association to schizophrenia for the Gria1 locus which codes for the GluA1 subunit of the AMPA glutamate receptor. GluA1 KO mice have previously been studied in relation to schizophrenia but, notably, striatal whole tissue levels of dopamine and its metabolites appear normal in these animals. However, we might not expect to see changes in dopamine activity in anaesthetised animals, or in a home-cage environment. Indeed, changes in phasic DA responses are likely to be both behaviour-dependent and stimulus-specific.

To test this possibility we have recorded phasic DA signals with high temporal resolution, in freely moving, behaving wild-type and GluA1 KO mice, using fast-scan cyclic voltammetry (FSCV). This state of the art electrochemical recording technique involves chronically implanting carbon-fibre microelectrodes into the nucleus accumbens to allow sub-second, real time measurements of DA, allowing definitive assessment of extracellular DA changes in terminal regions. Here we demonstrate that phasic dopamine signals in response to neutral light stimuli fail to habituate in Gria1-/- mice, resulting in a behaviourally relevant, hyper-dopaminergic phenotype in these animals. This parallels previous behavioural data from these mice. In addition, phasic dopamine responses to unsignalled rewards were also significantly enhanced in the knockout mice. Thus, we provide evidence for behaviourally-relevant hyper-dopaminergic responses in a genetically modified mouse model of glutamatergic dysfunction relevant to schizophrenia. These data may have important implications for understanding the aetiology of aberrant salience in psychotic disorders including schizophrenia.

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Poster number: P-T171
Theme: Psychiatry & mental health

Site-dependent effects of optogenetic stimulation in thalamic reticular nucleus on cortical states

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The corticothalamic loop has long been implicated in a range of neuropsychiatric diseases. The thalamic reticular nucleus (TRN), a part of the corticothalamic loop, plays a key role in selective attention and sleep spindles. Furthermore, sleep spindles are reduced in amplitude and duration in schizophrenia patients, implying clinical relevance of TRN functions. However, while the TRN is topographically organized, it remains unclear whether and how the TRN consists of functionally distinct sub-regions. Combining optogenetic and electrophysiological approaches in mice, we investigated changes in sleep spindles and EEG oscillations caused by optogenetic stimulations in different parts of the TRN. Archaerhodopsin (Arch), a light sensitive proton pump, was expressed specifically in either an anterior or posterior part of the TRN in parvalbumin (PV)-Cre mice using adeno-associated viral vectors. We found restricted expression patterns of Arch in PV-positive neurons of the TRN depending on injection sites. Effects of optical stimulation on cortical EEGs were assessed by delivering green light through chronically implanted optic fibers in up to 1 min periods in freely behaving animals. Tonic stimulations during awake states did not produce any significant change in EEGs whereas stimulations during sleep (mostly slow wave sleep) increased delta power and the number of sleep spindles . Together these data support the notion that activity in the TRN may have different impacts on the modulation of cortical states in a site-dependent manner.

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Poster number: P-T172
Theme: Methods and techniques

A novel microfluidic drug discovery platform for studying communication between synaptically connected neural networks

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Aims: Many in-vitro systems used during pre-clinical trials fail to recreate the biological complexity of the in-vivo neural microenvironment. Taking advantage of recent advances in microfluidic technology, we seek to develop a perfusion based drug discovery platform that is capable of high-throughput pharmacological profiling. This in turn will allow us to better understand how drugs influence the communication between functionally connected neural networks.
Methods: Mixed primary hippocampal networks were grown in microfluidic devices with environmentally separated chambers that allow synaptic connections to be formed with each other via an array of microchannels. The perfusion of multiple compounds in one chamber was achieved using computer controlled fluid actuation connected to the inlets/outlets of the microfluidic device. Responses to perfusates from directly stimulated neurons and those synaptically connected were recorded using calcium imaging.
Results: Following live/dead assays, a flow rate of 4µl min-1 showed the greatest cell viability and was used for subsequent experiments. Subsequently, a glutamate concentration response curve following direct stimulation was obtained which revealed an EC50 = 4µM. Pharmacological manipulation of neuronal activity was also achieved as the neuronal response to glutamate was reversibly reduced in the presence of ionotropic glutamatergic antagonists. Furthermore, repeated glutamate perfusions induced increasing levels of activity in the adjacent, naïve neural network.
Conclusion: The proposed microfluidic system is able to reliably produce pharmacological profiles for drugs in a neurological setting. The novelty of the presented drug discovery platform is its ability to not only determine the properties of a new drug, but how the drug influences communication between neural networks.

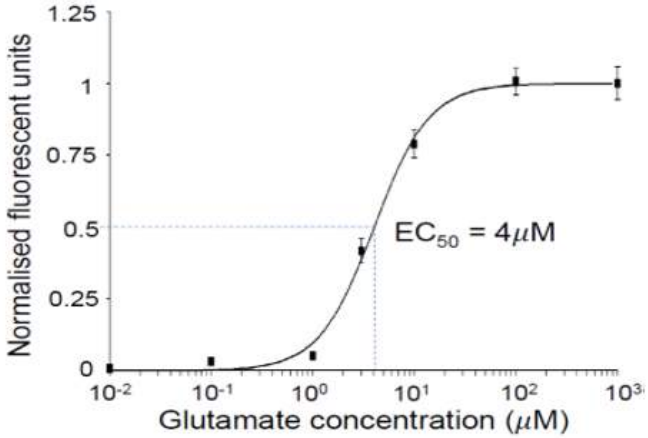

Figure 1: A concentration response curve produced following multiple glutamate perfusions reveals an EC_{50} of 4μM; n = 6 cultures, 14 devices, 184 cells.

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Poster number: P-T173
Theme: Methods and techniques

Neuroimaging assessment of cumulative experience in non-human primates

Authors: Colline Poirier, Alexander Thiele, Melissa Bateson - *Institute of Neuroscience Newcastle University*

Researchers have ethical and legal obligations to optimise the physical and emotional wellbeing of their animals. Furthermore, current European legislation places an emphasis on the animal's lifetime experience. However, current methods for assessing the

cumulative experience of animals are poorly validated and suffer from a lack of sensitivity and/or specificity. The general goal of this work was to develop and validate a new method to assess cumulative experience in non-human primates (NHPs).

Recent development in stress biology has shown that in rodents, NHPs and humans, the amount of grey matter in the hippocampus co-varies with the cumulative experience of individuals. These new findings open the possibility to use the amount of hippocampal grey matter as a biomarker of cumulative experience in laboratory animals. The hippocampus is not a homogenous region and its different functions seem to be spatially segregated. In this study, we tried to identify which part of the hippocampus is most sensitive to cumulative experience in NHPs.

As a proxy for cumulative experience, we used artificial weaning age (i.e. definitive separation from the mother forced by human caretakers). Early artificial weaning is a well-established early-life stressor in NHPs. It is also known to have long-lasting detrimental effects on emotionality, social, sexual and maternal behaviours, as well as growth, immune responses and in some cases survival, inducing a poorer life time experience in individuals weaned earlier. Eleven male adult macaques were scanned with a 4.7 T MRI scanner. In each subject, the amount of grey matter of each voxel comprised in the hippocampus was determined using voxel-based morphometry. After controlling for covariates including age and total brain size, a multiple regression analysis revealed a positive correlation between weaning age and the amount of grey matter in the right anterior hippocampus.

We argue that with appropriate strategies to control for potential confounding factors, the amount of grey matter in this specific part of the hippocampus can now be used to measure the cumulative experience of NHPs.

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Poster number: P-T174
Theme: Methods and techniques

Implementing hybrid circuits with StdpC, a flexible, easy-to-use dynamic clamp software

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Dynamic clamp is a closed-loop electrophysiology method that allows experimenters to inject voltage-dependent currents into a live neuron. The method relies on a high-frequency control loop that consists of measuring the membrane potential, calculating the corresponding current, and injecting it back into the cell. Dynamic clamp is often implemented using highly specialised real-time software and/or hardware, which requires significant technical aptitude to set up. In contrast, the Windows-based StdpC software runs on any commercial computer and is straightforward to set up and use.

StdpC offers a wide range of dynamic clamp related features. It is designed to simulate ionic conductances, chemical synapses, gap junctions, and any combination thereof, up to and including entirely virtual neuron models with synapses leading to and from real neurons. For each of these basic building blocks, several mathematical formulations are built-in, ready for the user to parametrise. Simulated synapses support advanced features such as spike-time dependent plasticity and delayed transmission. StdpC can be used with separate voltage-measuring and current-injecting electrodes, but it also includes an active electrode compensation algorithm that allows accurate clamping with a single (patch or sharp) electrode. Experiments can be automated via a scripting interface, and the openness and modular structure of the source code give users with some programming facility the option to quickly extend the software to suit their needs.

As an example for the application of StdpC, we present an experiment where we use hybrid circuits to investigate bistability in the visual system. Two pyramidal neurons in the primary visual cortex are patch-clamped simultaneously. They are then coupled through mutual disynaptic connections using models of different inhibitory interneurons in an effort to learn more about the bottom-up processes that may underlie the phenomenon of bistable visual perception.

First author's PhD funding provided by the University of Sussex School of Life Science.

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Poster number: P-T175
Theme: Methods and techniques

Clinical Acute Stroke Imaging of Motor Deficits using VLSM and White Matter Track Based Analyses

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Stroke is one of the most common causes of neurological disability in the Western World, yet little is understood about how motor deficits post-stroke can be predicted from lesions visible on acute clinical imaging. To address this question, we collected clinical computer tomography (CT) brain scans from 185 acute stroke patients (mean 1.93 days post stroke), along with measures of gross and fine motor skill within 5±4 days post stroke. We asked patients to perform a tap to their head and to pick up a pencil lying on a table with each hand separately. Results were scored on a scale of 1 to 4, designating a complete inability to a complete ability to perform the tasks.

Stroke lesions were manually delineated by trained technicians and were registered to a stereotaxic space using Clinical Toolbox (Rorden et al., 2012). To map the lesion affected-fiber tracts, disconnectome maps for each patient were generated using software from the BCBtoolkit (Thiebaut de Schotten et al., 2015). To further generate data on lesion-affected anatomy, patient lesion masks were overlaid with fiber tracks from a white matter atlas (natbrainlab.co.uk).

Of the 185 patients, 97 presented with minor to severe motor deficits, of whom 47 patients were unable to perform the task, 15 patients were only partly able to perform the task and 35 patients performed the task with minimal difficulty. The VLSM analysis using the task data and lesion masks localized the relationship between lesion site and motor deficit to a single cluster in the right posterior limb of the internal capsule. Using this identified cluster as a seed region, further analyses on intersecting tracks were performed allowing for groupings on the basis of affected tracks. Despite the laterality of the above mentioned VLSM results, patients with damage to the left (n=20) and right (n=22) corticospinal tracts were significantly worse at the motor tasks than those without lesions in these tracks (ps<0.001). When analyzing the motor data in a VLSM analysis with the disconnectome maps, significant relationships between motor deficit and lesion location was demonstrated in bilateral motor related regions. The results from this study demonstrate different approaches for comparing lesion affected anatomy and behavioral deficits.

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Poster number: P-T176
Theme: Methods and techniques

Rhythm of the light: The design and validation of novel voltage sensitive dyes using the stomatogastric ganglion of Cancer pagurus

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Voltage sensitive dyes (VSDs) offer an alternative to Ca2+ sensitive dyes for the imaging of neuronal networks. The time-resolution of VSDs is faster compared to Ca2+ imaging, but their signal to noise ratio (SNR) is ~10 times less that of Ca2+ dyes. This work aims to improve the SNR of VSDs while maintaining their dynamics through the design of VSDs derived from Bodipy dyes (e.g. JULBD) that were shown as viable alternatives to standard VSDs (e.g. di4-ANEPPs)[1].

The stomatogastric ganglion (STG) of the brown crab (Cancer pagurus) is one of the most researched small biological nervous systems due to the relative large size and accessibility of the neurons located within the STG and its robust pyloric rhythm (PR) which controls the movement of muscles in the gastric system. Optical imaging of the STG using VSDs has been well studied (e.g. [2]), allowing the simultaneous recording of the electrical activity of many cells.

The toxicity (indicated by the increase in PR frequency) of 4 novel dyes (NDS3, NDS4, NDS8, SC114), di4-ANEPPs and JULBD (as baseline measures) was assessed. The STG was removed and desheathed, each dye bath applied for 20min followed by 20min washout. For each dye, the duration of light shone onto the STG ranged from 20s to 5mins in increments of 20s. di4-ANEPPs caused an increase in the PR (20-100s), before saturating (120-220s) and then returning to baseline (240s+) (N=5). JULBD increased by 60s light exposure, before disrupting the PR at 100s+. Initial results indicate that NDS3, 4 and 8 had no effect on the PR, while SC114 appeared to slow it (N=1 for last 5 VSDs, Figure 1).

Future work involves the further validation of these dyes, assessing toxicity and SNR, the results of which will feedback into design refinement of the structure of suitable dyes.

[1] Bai, D., Benniston, A.C., Clift, S., Baisch, U., Steyn, J., Everitt, N. and Andras, P., 2014. Low molecular weight Neutral Boron Dipyrromethene (Bodipy) dyads for fluorescence-based neural imaging. Journal of Molecular Structure, 1065, pp.10-15.

[2] Städele, C., Andras, P. and Stein, W., 2012. Simultaneous measurement of membrane potential changes in multiple pattern generating neurons using voltage sensitive dye imaging. Journal of neuroscience methods, 203(1), pp.78-8.

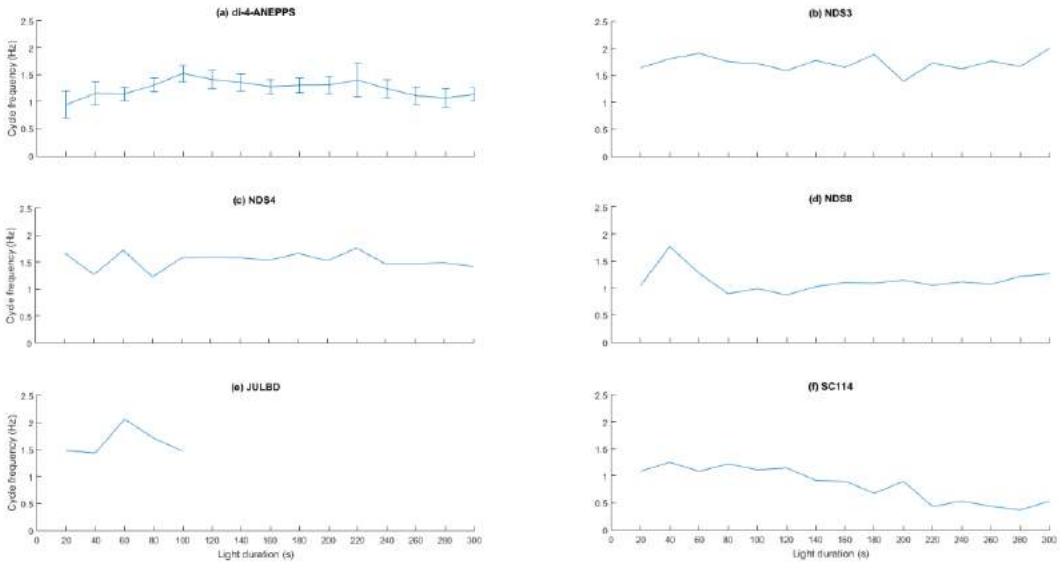

Figure 1. The results of the toxicity evaluation experiments with established and candidate voltage sensitive dyes.

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Poster number: P-T177
Theme: Methods and techniques

Recursive fast search and find of density peaks algorithm for spike-sorting from extracellular neuronal recordings

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In vivo and in vitro extracellular neuronal recordings consist of local field potential and a mixture of action potentials, or spikes, from many neurons. It is necessary to isolate or sort the activity of individual neurons to study their cellular dynamics and response to external or internal stimuli. This process is known as spike-sorting. Spikes are detected, i.e. using a voltage threshold, and their features, e.g. waveform properties, are extracted. These features from individual neurons form dense regions or clusters in their distributions as they follow similar properties. The clusters are isolated either manually or by automated clustering algorithms. Most of the clustering algorithms for spike-sorting are based on the principle that cluster data points are Gaussian-distributed. But features like amplitude of the spikes often do not follow such distribution due to, for example, detection using amplitude threshold. Here, we used a density-based clustering algorithm to recursively isolate spiking activity of neurons of varying firing rates irrespective of the distribution patterns. It is based on the idea that cluster centres have high density and they are located far away from points of higher densities. The rest of the feature data points are assigned to the same cluster as of their nearest neighbour of higher density. Modality of the clusters were determined from the peaks in the kernel-based probability estimates, unimodal clusters were isolated, and the rest of the data points followed the recursion of the above algorithm. We show that the algorithm

can effectively sort spikes of varying firing rates and can overcome the limitations of using centroid-based, e.g. k-means, or other density-based, e.g. DBSCAN, clustering algorithms. It may also be used to identify clusters in other biological data, i.e. clustering of DNA- or RNA-sequences, as the algorithm relaxes the assumption about the underlying data distribution function.

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Poster number: P-T178
Theme: Methods and techniques

Visualization of specific mRNAs and lncRNAs within morphological context in the nervous system using the RNAscope® in situ hybridization assay

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Neuroscience is one of the fastest growing interdisciplinary research fields that studies the central (CNS) and peripheral nervous system from the molecular and cellular levels to the systems level. Areas of research include neural development, structural and functional organization of the nervous system, cognitive and behavioral neurosciences, and clinical neurosciences including neurodegenerative diseases.

The RNAscope® assay provides a powerful method to detect gene expression within the spatial and morphological tissue context. The proprietary “double Z” probe design in combination with the advanced signal amplification enables a highly specific and sensitive detection of the target RNA with each dot visualizing a single RNA transcript. Therefore, this robust signal-to-noise technology allows for detection of gene transcripts at single molecule level with single-cell resolution analysis and can further expand our understanding of gene expression in cell lines and tissues samples. The multiplexing capabilities of both the chromogenic and fluorescent RNAscope® assays facilitate the simultaneous visualization of multiple targets in formalin-fixed paraffin-embedded (FFPE) and fresh frozen samples, enabling consistent characterization of cell populations within the nervous system. In summary, RNAscope® technology allows the visualization and quantification of virtually any gene from any genome in any tissue with unprecedented specificity and sensitivity.

Here we illustrate the utility of RNAscope® applications in neuroscience:
• Identification, characterization, and (co-) localization of both mRNAs and lncRNAs in the nervous system
• Identification, visualization and characterization of specific cell types in the nervous system
• Detection of mRNA in the nervous system when no (reliable) antibodies are available
• Visualization of neuronal network activity and plasticity
• Validation of target mRNA expression after high-throughput gene expression analysis
• Validation of (cell type-specific and conditional) genetic modifications.

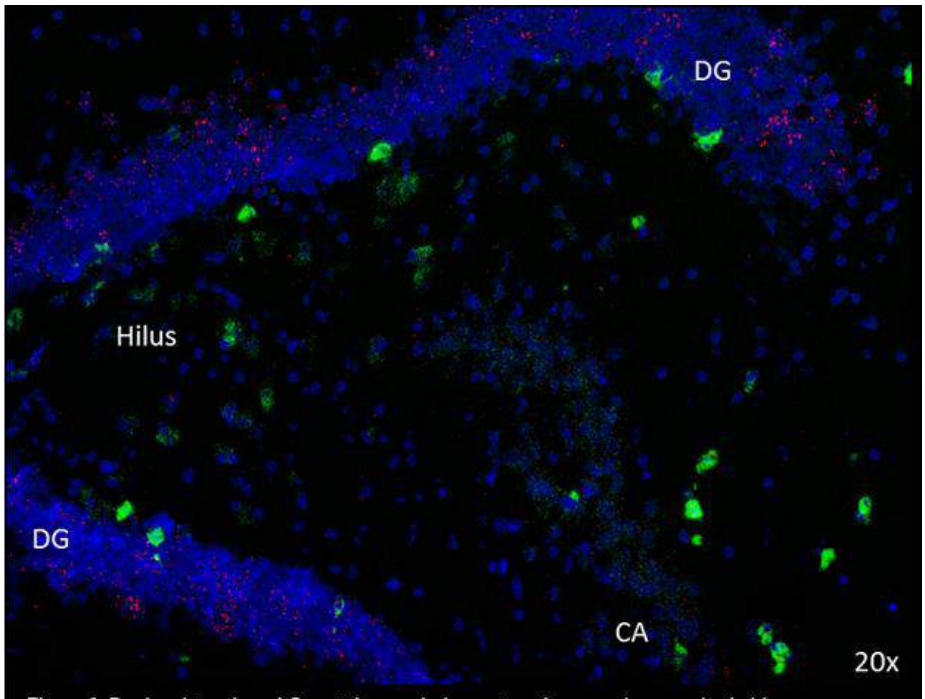

Figure 1: Duplex detection of G protein-coupled receptors in normal mouse brain hippocampus using the RNAscope® Multiplex Fluorescent assay on Fresh Frozen tissue samples: Cannabinoid Receptor 1 (Cnr1, Green) and Dopaminergic Receptor D1 (Drd1, Red). Cells are counterstained with DAPI. CA = Cornu Ammonis DG = Dentate Gyrus.

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Poster number: P-T179
Theme: Methods and techniques

Accelerated brain simulations with GeNN

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When simulating models of neural networks in the brain, the size of the simulated networks matters. Modern technology such as Graphical processing Unit (GPU) accelerators can help Neuroscience researchers to simulate larger and more realistic brain models. Here we present the GPU enhanced neuronal networks (GeNN) framework [1,2] that we have created to gain the most from GPU accelerators. GeNN is using an approach of automatic code generation from straightforward model descriptions provided by the scientist to generate code that is optimized for the detected GPU accelerator and the defined model. The technical difficulties of using GPU accelerators are hence removed from users who can concentrate on interesting scientific questions instead. At the same time, GeNN remains flexible and expert users can manipulate virtually every aspect of the simulations. GeNN supports all typical computational neuroscience models by allowing users to define their own equations for the model elements, such as neuron dynamics, synapse updates and learning rules. GeNN has been used for networks of Hodgkin-Huxley neurons, with Hebbian learning, STDP and 3-factor learning rules, as well as for more simple models such as networks of Izhikevich, integrate-and-fire and Rulkov map neurons.

For less expert users, we have created additional interfaces to the SpineCreator graphical model definition interface [3] and to the popular Brian 2 simulator [4]. With the latter, it is as simple as issuing the command set_device('genn') to take advantage of GPU acceleration.

Acceleration compared to traditional CPU-based solutions varies by model and GPU accelerator hardware and can be as high as 200 times but also as low as none. GeNN is available as open source software under GPL v2 [2].

1. E. Yavuz, J. Turner and T. Nowotny (2016). GeNN: a code generation framework for accelerated brain simulations. Scientific Reports 6:18854. doi: 10.1038/srep18854
2. GeNN, http://genn-team.github.io/genn/, accessed 2016-12-15
3. SpineCreator, http://bimpa.group.shef.ac.uk/SpineML/index.php/SpineCreator_-_A_Graphical_Tool, accessed 2016-12-15
4. Brian 2, https://github.com/brian-team/brian2, accessed 2016-12-15

This work was partially financed by the EPSRC, grant EP/P006094/1.

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Poster number: P-T180
Theme: Methods and techniques

Identification of neural responses to human faces using wireless multichannel EEG recordings

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Previous fMRI and EEG studies have shown face-specific neural responses to faces compared to objects. Detection of face-specific brain activation in freely behaving and moving people has not been accomplished as of yet. The purpose of our research was to identify, using wireless multichannel EEG in freely moving participants, event-related potentials (ERPs) during viewing human faces.

Mobile EEG and eye tracking was recorded from 19 freely moving participants whilst they viewed a mock art gallery. Stimuli were presented on 20 panels (A0 poster size) displayed in the ground floor of the psychology department building of the University of Liverpool. Positive, negative and neutral valence images were viewed and later rated by the participants. EEG was recorded continuously using a 64-channel BrainProduct MOVE system. In absence of triggers indicating onsets of viewing of visual stimuli, a novel PupilLab head-mounted wearable eyetracker was used to capture real world video recordings and the calibrated XY locations of the gaze. After synchronising the time sources of EEG and eye-tracking recordings, BESA 6.1. program was used to process EEG data.

Wireless EEG recordings allowed identification of a face-related ERP component in the latency interval ranging from 165 to 210 ms (N170 potential); this component was not seen whilst participants were viewing non-living objects. The face ERP component was sensitive to the emotional face expression; in particular, the amplitude of N170 potential was stronger during viewing disgusted compared to neutral faces. Source dipole analysis revealed three equivalent current dipoles in the latency interval from 100 ms to 300 ms. Two source dipoles, located in the left extrastriate (BA19) and primary visual (BA17) cortex, modelled the visual P100 component, and one equivalent current dipole, fitted to the right fusiform gyrus (BA37), accounted for the face-related N170 potential.

This study is the first to demonstrate the face-related ERPs in freely moving individuals in natural settings. The study opens new possibilities in clinical, developmental, social or marketing research in which information about presence of face perception and the type of perceived facial expression is of importance.

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Poster number: P-T181
Theme: Methods and techniques

Modification of postsynaptic genes using CRISPR/Cas9 system

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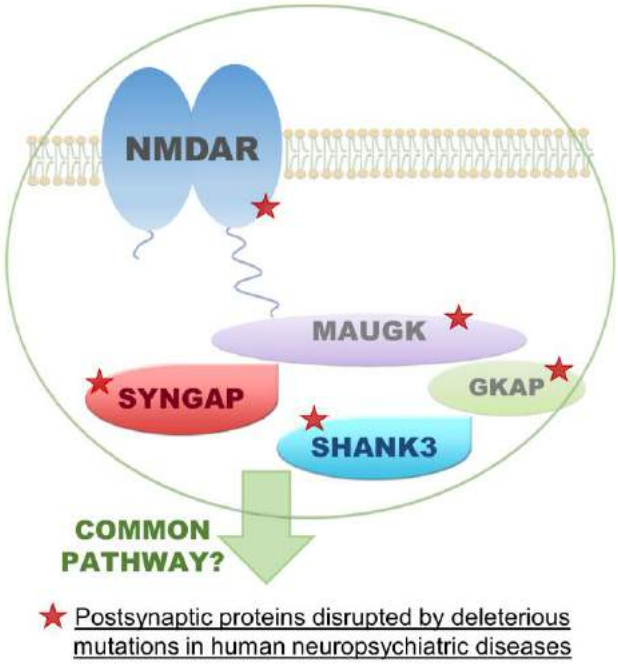
The N-methyl-D-aspartate receptor (NMDA receptor) and its interacting proteins constitute large macro-molecular complexes (NMDAR complexes) at excitatory synapses1. Recent human genomic studies discovered several mutations in the genes encoding the components of NMDAR complexes in various neuropsychiatric disorders including intellectual disability (ID), autism and schizophrenia. However, little is known about how mutations in these genes alter molecular and cellular pathways leading to pathological phenotypes. To answer the question, our lab has been systematically mutating synaptic genes in mice using conventional gene targeting methods. To further accelerate generation of mutants we adapted CRISPR genome editing system in mouse embryonic stem (ES) cells.

SH3 and multiple ankyrin repeat domains 3 (Shank3) is a crucial scaffolding protein of NMDAR complexes and is indicated in autism2 and schizophrenia3. CRISPR-induced knockout mutation of Shank3 was successfully introduced in ES cells, and these cells were injected into blastocysts and 3 chimaeras were born. These chimaeras then were crossed with wild-type mice and germline transmission was confirmed. Having established a knockout mutation using CRISPR, we moved on to modify Synaptic GTPase-

activating protein (SynGAP), another component of NMDAR complexes. De novo mutations of SynGAP have been found in ID4, autism4 and schizophrenia5. To introduce a defined mutation in SynGAP gene, we designed a CRISPR-mediated point mutation, and obtained ES cells with the precise mutation. Here we demonstrate CRISPR facilitates the disruption of Shank3, as well as the precise editing in SynGAP in mouse ES cells with high efficiency.

Reference:
1. Frank et al. Nat. Commun. 7, 11264 (2016).
2. Durand et al. Nat. Genet. 39, 25–27 (2007).
3. Gauthier et al. Proc. Natl. Acad. Sci. 107, 7863–7868 (2010).
4. Berryer et al. Hum. Mutat. 34, 385–394 (2013).
5. Purcell et al. Nature 506, 185–90 (2014).



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