Symposium 1 – Neural networks of fear and anxiety
Theme: Attention, motivation, behaviour

1.01. Neural mechanisms of post-traumatic stress disorder as seen through stress-enhanced fear learning

Professor Michael Fanselow – *UCLA, USA*

I will describe how exposure to stress causes a nonassociative sensitization of future fear learning. This stress-enhanced has some correspondence to the symptomatology of PTSD. I will go on to describe the necessary but not sufficient role of corticosterone in inducing this sensitization. I will conclude with a description of how changes in the nature of glutamate signaling provide the basis for expression of stress-enhanced fear learning.

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1.02. Prefrontal oscillatory mechanisms of fear behaviour

Mr Nikolas Karalis - *Ludwig-Maximilians University, Munich*

The medial prefrontal cortex (mPFC) is believed to regulate fear behaviour via projections to the amygdala, a neuronal structure encoding associative fear memories. Recent converging evidence suggest that the expression of conditioned fear and extinction memories relies on the coordinated activity between the mPFC and the basolateral amygdala (BLA).

Precise spike timing through the coordination and synchronization of neuronal assemblies is an efficient and flexible coding mechanism that is widely employed in the brain for sensory and cognitive processing. Decades of research have identified neural oscillations as a mechanistic substrate for the formation of cell assemblies and the coordination of information transfer between remote brain regions.

However, to date, the mechanisms allowing the long-range network synchronization of neuronal activity between the mPFC and BLA during fear behaviour remain virtually unknown.

Using a combination of extracellular recordings and optogenetic manipulations, we investigated the oscillatory and temporal coding mechanisms mediating mPFC-BLA coupling during fear behaviour.

We found that freezing, a behavioural expression of fear, is tightly associated with an internally generated brain state that manifests in sustained 4 Hz oscillatory dynamics in prefrontal-amygdala circuits. 4 Hz oscillations accurately predict onset and termination of the freezing state. These oscillations synchronize prefrontal-amygdala circuits and entrain neuronal activity to dynamically regulate the development of neuronal ensembles. This enables the precise timing of information transfer between the two structures and the expression of fear responses. Optogenetic induction of prefrontal 4 Hz oscillations promotes freezing behaviour and the formation of long--lasting fear memory, while closed-loop phase specific manipulations bidirectionally modulate fear expression.

Our results unravel a physiological signature of fear memory and identify a novel internally generated brain state, characterized by 4 Hz oscillations. This oscillation enables the temporal coordination and information transfer in the prefrontal-amygdala circuit via a phase-specific coding mechanism, facilitating the encoding and expression of fear memory.

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1.03. Neural mechanisms underlying recurrent fear memories in post-traumatic stress disorder

Dr Sarah Garfinkel - *University of Sussex, UK*

Posttraumatic Stress Disorder (PTSD) is associated with persistent and recurrent fear memories. It has been hypothesized that individuals with PTSD cannot effectively use contextual information to guide appropriate memory expression. Here we detail evidence of impaired contextual processing in veterans with PTSD relative to Combat Control veterans. Using a two-day fear conditioning paradigm with concurrent fMRI, both veteran groups were able to successfully acquire and extinguish conditioned fear responses (coloured lights initially paired with shock, occurring in a danger and safety context respectively). On day two, contextual information successfully modulated memory expression in the Combat Control individuals, with the safety (extinction) memory prevailing in the safety context, and the original fear memory prevailing in the danger context. In contrast, PTSD individuals were impaired in their capacity to use contextual information to guide appropriate memory expression. These findings suggest that

excessive fear expression in PTSD may be maintained through altered vmPFC-hippocampal-amygdala circuits involved in emotional memory and contextual processing.

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1.04. Cerebellar and periaqueductal grey contributions to fear behaviour

Dr Charlotte Lawrenson - *University of Bristol, UK*

Brain regions such as the amygdala, prefrontal cortex, hippocampus and periaqueductal grey (PAG) play an important role in fear behaviour. The talk will present evidence that the cerebellum should also be added to this network. In the rodent, electrophysiological mapping has shown that neuronal connections exist between the PAG and cerebellum (Koutsikou et al, 2014). The PAG is well known for its role in survival circuits and controls the expression of fear-induced freezing behaviour, cardio-respiratory responses and ultrasonic vocalisations. The amount of freezing is often used as a measure to quantify fear and in rats freezing can be initiated innately e.g. via the predator odour test, or can be learned e.g. via auditory cued fear conditioning. Lesioning studies targeting the pyramis of the cerebellum disrupted innate and fear-conditioned freezing behaviour in the rat showing the cerebellum also plays a role in the expression of fear (Koutsikou et al, 2014). Furthermore, inhibition of the PAG modulates transmission in spino-olivocerebellar projections, but also the excitability of spinal motor circuits, determined by changes in H reflexes (Koutsikou et al, 2015). To investigate PAG-cerebellar connectivity further our current experiments are recording from both brain regions simultaneously during fear behaviour. Tetrodes have been implanted into the medial cerebellar nucleus and contralateral PAG of rats to record local field potential (LFP), event related fields cued to tones and unit activity. For example, following auditory cued fear conditioning an increase in theta LFP activity (4-10Hz) in the cerebellar nuclei occurs during presentation of the conditioned tone, and there is also an increase in gamma LFP activity (40Hz) related to freezing. The gamma activity also occurred during freezing elicited by cat odour. These preliminary results suggest that significant changes in neural dynamics occur related to cerebellar processing during conditioned and innate fear behaviour. This research was funded by the Biotechnology and Biological Sciences Research Council UK and the Medical Research Council.

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Symposium 2 – Spinal motor control: more than just a reflex

Theme: Sensory and motor systems

2.01. Descending control of bilateral circuits controlling limb movement

Professor David Maxwell - *University of Glasgow, UK*

Descending systems have a crucial role in the selection of motor output patterns by influencing activity of interneuronal networks in the spinal cord. Premotor commissural interneurons (PCIs)
that project to the contralateral grey matter are essential components of such networks as they coordinate left-right motor activity of fore- and hind-limbs. Although there has been a focus on the role of PCIs in locomotion they also serve other functions including the coordination of reaching and grasping activity of forelimbs. PCIs form heterogeneous populations and may be classified according to a variety of criteria. In the cat midlumbar spinal cord we have identified 4 populations of PCIs1: 1) Inhibitory deep dorsal horn cells activated by GpII muscle and cutaneous afferents along with the corticospinal tract (CST) which project bilaterally; 2) Excitatory cells in the intermediate grey matter that are co-activated by GpI and II muscle afferents along with CST, reticulospinal (RST) and rubrospinal tracts which project either bilaterally or contralaterally; 3) Lamina VIII cells activated by GpII afferents that project contralaterally and are a mixed excitatory and inhibitory population; 4) Lamina VIII cells activated by the RST that project contralaterally and are a mixed excitatory and inhibitory population. Although we have considerable knowledge of the organisation of PCIs in lumbar spinal cord, information regarding their organisation in cervical regions by comparison is limited. Recently we performed a series of experiments in the rat cervical spinal cord2 to examine the organisation of PCIs and their relationship with descending systems. The results showed that PCIs receive very few contacts from CST terminals but large numbers of contacts are formed by RST terminals. Cervical PCIs received about 80% excitatory and 20% inhibitory RST contacts. Therefore, in the rat, the CST appears to have minimal direct influence on cervical PCIs but the RST is likely to have a powerful influence. Therefore, the RST may be the dominant descending pathway for bilateral coordination of forelimb activity in the rat. Supported by the MRC and NIH.

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2.02. Bilateral organisation in the primate cervical spinal cord

Dr Demetris Soteropoulos - *University of Newcastle, UK*

Most everyday movements require the bilateral co-ordination of limbs on either side of the body. This applies to relatively 'automated' movements such as locomotion, but also to more object oriented actions, where an object is manipulated by both hands together. Although it is well established that the spinal cord has a critical role to play for locomotion, for manipulative movements the emphasis is on the importance of higher motor centres such as the primary motor cortex. While higher motor centres are indeed critical, there is increasing evidence that the spinal cord also makes contributions to voluntary movements [1, 2]. Some of our recent work has highlighted that like the lumbar cord, cervical spinal circuits also show substantial degree of bilateral organisation [3], but their role during bimanual movements is far from clear. We will discuss how spinal cord circuits in the cervical cord could contribute to bimanual actions. Sensory information from both hands can impact spinal circuits and we will discuss how this could shape neural activity during movement. During a bimanual task that requires either or both hands to carry out reaching and grasping movements, primate spinal cord interneurons are not only highly active but show activity patterns that take into account the bimanual context of the movement. When this activity is compared to that of cells in the primary motor cortex for the same task, the activity of spinal circuits is much less lateralised than that of cortical cells. How this fits with current models of bimanual control will be discussed.

Funded by the MRC and BBSRC.

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3) Soteropoulos DS, Edgley SA, Baker SN. Spinal commissural connections to motoneurons controlling the primate hand and wrist. J Neurosci. 2013 Jun 5;33(23):9614-25.

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2.03. Combinatorial approaches to promoting recovery of limb function in rats with chronic spinal cord injury

Dr Ronaldo Ichiyama - *Leeds University, UK*

Spinal cord injuries often result in compromised sensorimotor and autonomic functions below the level of lesion. For several years, different groups have demonstrated that the spinal cord below the level of the injury can generate functional movements when provided with appropriate physiological conditions such as with locomotor training and rehabilitation (Lovely et al., 1986; Barbeau and Rossignol, 1987). For example, we have previously demonstrated in a complete spinal transection model that epidural electrical stimulation of the lumbar cord enables intraspinal circuitry to produce coordinated weight bearing steps which is driven by afferent input (Ichiyama et al., 2005). With the advent and development of promising new neuroregenerative interventions a new environment of enhanced plasticity can now be induced to facilitate functional recovery. We have also previously demonstrated that activity-driven plasticity must be carefully combined and delivered because it can result in detrimental effects. We will discuss results from experiments demonstrating different degrees of functional motor recovery following different interventions (epidural stimulation, locomotor training, anti-Nogo-A antibody, chondroitinase ABC) in severe incomplete spinal cord injuries. The capacity of lumbar spinal circuits to control locomotor behaviours will be highlighted. Our results strongly suggest that when plasticity is enhanced after lesions to the spinal cord, activity must modulate formation and consolidation of synapses to result in functional movements. The emergence of a critical role for neurorehabilitation in this context will be discussed.

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2.04. Plasticity in the Corticospinal Pathway after Human Spinal Cord Injury

Dr Monica Perez - *The Miami Project to Cure Paralysis, USA*

The corticospinal tract is an important target for motor recovery in humans with spinal cord injury (SCI). Here, I will discuss novel paired stimulation protocols aiming at enhancing corticospinal transmission and residual voluntary motor output in humans with partial paralysis due to cervical incomplete chronic SCI. In a first protocol, we used paired transcranial magnetic stimulation (TMS) pulses precisely timed to increase the amplitude of motor evoked potentials at interstimulus intervals compatible with the later I-waves (I3) recorded from the epidural space. In a second protocol, we precisely timed the arrival of descending and peripheral volleys at corticospinal-motoneuronal synapses of an intrinsic finger and a lower-limb muscle. Presynaptic volleys elicited by TMS were timed to arrive before or after depolarization of spinal motoneurons elicited by peripheral nerve stimulation. Both protocols resulted in distinct improvements in different aspects of corticospinal transmission and voluntary motor output. Thus, tailored stimulation of the corticospinal pathway may present a novel therapeutic tool for enhancing voluntary motor output following SCI.

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Symposium 3 – Novel targets for pain, depression and their co-morbidity

Theme: Novel treatments and translational neuroscience

3.01. Reciprocal interactions between pain and negative effect: Role of the endocannabinoid system

Professor David Finn - *National University of Ireland, Galway*

Pain and affective state interact reciprocally, whereby the latter can both influence, and be influenced by, the pain experience. Wistar-Kyoto rats exhibit an anxiodepressive phenotype and also display hyperresponsivity to noxious stimuli. These effects are associated with alterations in levels of endocannabinoids and related N-acylethanolamines and altered expression of their receptor targets or metabolizing enzymes in brain regions regulating pain and affect. Pharmacological blockade of the CB1 receptor exacerbates hyperalgesia to persistent inflammatory pain in Wistar-Kyoto rats, while pharmacological blockade of endocannabinoid degradation attenuates hyperalgesia. Additional data suggest an important role for the endocannabinoid system in the periaqueductal grey and rostral ventromedial medulla in the Wistar-Kyoto model of hyperalgesia associated with negative affective state. Our results also suggest an important role for TRPV1 and PPAR? in the periaqueductal grey in the Wistar-Kyoto model. Further evidence that deficits in the functionality of the descending inhibitory pain pathway likely underlie the hyperalgesic phenotype of Wistar-Kyoto rats comes from our recent data suggesting that these rats exhibit impaired expression of fear-induced analgesia. Interestingly, induction of neuropathic pain in the Wistar-Kyoto rat (L5 spinal nerve ligation) is associated with significantly increased anxiety- and depressive-like behaviour compared with Sprague-Dawley counterparts, results which may be due, at least in part, to deficits in endocannabinoid signalling. This result maps onto clinical data that we and others have generated indicating increased anxiety and depression in neuropathic pain patients. Our work also points to a role for non-CB1 receptor targets of endocannabinoids and N-acylethanolamines in the affective dimension of pain, particularly in higher brain centres including the medial prefrontal cortex. These targets include peroxisome proliferator activated receptors (PPARs) and GPR55. Increased understanding of the neurochemical and receptor mechanisms underpinning pain-affect interactions may facilitate identification of novel therapeutic targets for the treatment of pain, affective disorders, and their co-morbidity.

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3.02. The microbiota gut brain axis as a key regulator of visceral pain

Dr Siobhan O'Mahony - *University College Cork, Ireland*

Visceral pain is a significant and prevalent feature of several disorders including the functional gastrointestinal disorder, irritable bowel syndrome (IBS). Treatment strategies are limited and often unsatisfactory which has opened up new research avenues into the aetiology of visceral pain. This research has led to an increased appreciation of the role of the microbiota gut brain axis in modulating viscera pain responses. More recently, the interactions between the gut microbiota and the central nervous system have emerged indicating that visceral pain related disorders may be prospective candidates for symptom relief via microbial manipulation. There is now recent work to highlight the enormous and exciting potential the gut microbiota has for visceral pain in the context of IBS and disorders of early life such as infantile colic.

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Conflicts of interest: The author has no conflict of interest.

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3.03. Treating chronic pain by inhibiting the stress regulator FKBP51

Dr Sandrine Geranton - *University College London, UK*

Stress can have dramatic effects on our pain experience and, while the neurobiological mechanisms that underlie these effects remain poorly understood, stress-regulated genes are likely to be involved.

We have recently identified a novel important target for the treatment of chronic pain: the stress regulator FKBP51 [1]. FKBP51 is up-regulated following activation of the glucocorticoid receptor (GR) by steroid hormones upon stress exposure. In a negative feedback loop, FKBP51 modulates GR sensitivity and therefore has a significant influence on the duration and intensity of the stress response. Supporting this mechanism, genetic variants in FKBP5 linked with higher levels of FKBP51 expression are associated with major depression and post-traumatic stress disorder in humans [2].

Here, I will discuss our recent findings that suggest that FKBP51 is a significant driver of chronic pain states. We have found that mice with global deletion of the gene FKBP5 do not develop mechanical hypersensitivity to the same extent as wild-type animals in a variety of models of long-term pain states. Crucially, local silencing at spinal level of FKBP51, using siRNA or pharmacological blockade with the state-of-the-art inhibitor SAFit2, can reduce the severity of established persistent pain states. This strongly suggests that FKBP51 can regulate chronic pain states independently from its role of mood regulator, presumably occurring at brain level. I will also present our preliminary findings suggesting that FKBP51 regulates long-lasting pain states by modulating glucocorticoid signalling. Finally, I will discuss the idea that modulation of FKBP51 by epigenetic mechanisms, in particular DNA methylation, might be responsible for the increased susceptibility to chronic pain seen in some individuals.

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We have no conflict of interest to declare.

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3.04. Dual basis for the anti-nociceptive action of SNARE proteases of botulinum neurotoxins: inhibition of the exocytosis of pain mediators and transducers

Professor Oliver Dolly - *Dublin City University, Ireland*

The many forms of intractable chronic pain, a major societal and financial burden, require non-addictive and effective medicines with prolonged action. Botulinum neurotoxin type A (BoNT/A) has shown promise in easing some types of pain in certain patients. Although this accords with its inhibition of K+-evoked release of calcitonin gene-related peptide (CGRP) from rat sensory neurons(1), suppression of the inflammation normally associated with pain has not been established. Our recent findings(2)

demonstrate that a pro-inflammatory cytokine, tumour necrosis factor alpha (TNFα), greatly elevates the appearance on sensory neurons of transient receptor potential (TRP) A1 and V1 channels, membrane proteins pivotal in transducing sensory signals. This involves their movement to the surface via CGRP-containing vesicles, a process found to be dependent on SNAREs and Munc 18-1. Knock-down of the latter or inactivation of SNAP-25, syntaxin 1 and vesicle-associated membrane protein 1 by requisite BoNT serotypes reduced the increases in surface content of the TRP channels, without affecting the basal pre-stimulation levels. Likewise, the TNFα-raised Ca2+-influx elicited by their agonists could be abolished by BoNT/A. These collective findings imply that BoNT/A exerts a dual action in normalising the pain-induced increased exocytotic delivery of TRP channels onto sensory neurons, and inhibiting the SNARE-dependent release of CGRP. This relates to mechanical and cold hyper-sensitivities being alleviated in a rat model of neuropathic pain after an intraplantar injection of BoNT/A.

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Symposium 4 – Hypothalamic tanycytes, the metabolic brain and adult neurogenesis

Theme: Neuroendocrine and autonomic nervous systems

4.01. Context-dependent modulation by hypothalamic tanycytes of the arcuate neuronal network controlling appetite

Dr Matei Bolborea - *University of Warwick, UK*

Hypothalamic tanycytes are glial cells lining the third ventricle of mammalians' brain. Recently, we have demonstrated that these cells play an important role into the regulation of body weight by sensing the cerebrospinal fluid (CSF) of nutrients such as glucose and amino acids, using influx of extracellular Ca2+ into the cell. This mechanism relays on tanycytic ATP release. These cell-sensors contact the CSF of the third ventricle, and send processes into the hypothalamic nuclei that control food intake and body weight.

How tanycytes pass on the metabolic message to the central nuclei of feeding is not yet described. We proposed thus to investigate the neural network that involves tanycytes nutrient sensing and neurones regulating the appetite.

We used optogenetic tools, to remotely activate tanycytes and mime responses to nutrients.

We observed that optostimulation of tanycytes in acute hypothalamic slices induces depolarisation of neurones of the arcuate nucleus. To a greater extend, tanycytes can also induce network changes by increasing the frequency of spontaneous synaptic potentials. Both phenomena were observed in neuropeptide Y-expressing (NPY) and proopiomelanocortin-expressing (POMC) neurons.

We also demonstrated that ATP release by tanycytes is also the transmitter that allows these neuronal responses.

Furthermore, according to the metabolic state tanycytes do not induce similar responses and the network effect appears to be altered only within POMC-expressing and unchanged in NPY-expressing neurons.

This is the first description of the hypothalamic neural network involving tanycyte-neuron communication.

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4.02. Hypothalamic stem cells and neurogenesis

Professor Marysia Placzek - *University of Sheffield, UK*

Recent evidence has shown that adult neurogenesis is sustained in the hypothalamus, a region of the brain that is the central regulator of homeostasis. A number of cell types appear to act as hypothalamic neural stem/progenitor cells, including tanycytes, radial-glial like cells that line the 3rd ventricle. We have investigated some of the molecular mechanisms governing tanycyte development, and will describe studies that suggest how developmental programmes can be sustained over the lifecourse. to

provide stem/progenitor cells and so a plasticity that underlies allostasis. We will describe current studies in which we are analysing the response of alpha-tanycytes to glucocorticoids, and asking how glucocorticoids provoke long-term changes in the hypothalamus

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4.03. The role of tanycytes in energy homeostasis and stability

Dr Jo Lewis - *University of Nottingham, UK*

Maintenance of energy homeostasis and seasonality requires the brain to monitor circulating concentrations of metabolites and hormones. These must cross the blood brain barrier to integrate with higher-order brain nuclei which then orchestrate an appropriate whole-body response. The resurgent interest in hypothalamic tanycytes is based on their potential to communicate with the cerebrospinal fluid, circulation and hypothalamic neurons, as their elaborate projections adjoin key nuclei implicated in energy homeostasis and seasonality. Indeed tanycytes have been implicated in the pathophysiology of leptin resistance and ghrelin uptake. Our studies provide evidence that tanycytes are an integral part of the mechanism which facilitates annual cycles of physiology and behaviour in seasonal mammals. It was previously shown that antibody-mediated targeting the FGFR1c, the primary receptor for FGF21, reduced body weight, adiposity and insulin resistance in mouse models of obesity and T2DM. We have demonstrated via in situ hybridisation studies a high level of expression of the FGFR1c in tanycytes in the Siberian hamster. Targeting of the FGFR1c with a monoclonal antibody in the long day (LD) obese Siberian hamster either peripherally or centrally via intracerebroventricular infusion reduced food intake and body weight. This was associated with a decrease in expression of type II iodothyronine-5'-deiodinase (DIO2) in the ependymal cell layer containing tanycytes. This enzyme governs the local generation of active thyroid hormone (T3) in tanycytes and the surrounding hypothalamus, a hormone known to be a major driver of seasonal cycles of energy balance. This supports the hypothesis that tanycytes are an important component of the mechanism by which the hypothalamus integrates central and peripheral signals to regulate energy homeostasis. Furthermore, we observed an attenuated response to targeting of FGFR1c in short day (SD) lean animals, further emphasising a role for tanycytes in seasonal cycles. Investigating tanycyte biology in the context of seasonal cycles of weight gain and loss should be beneficial to our understanding of their role in nutrition sensing and energy homeostasis.

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4.04. Modulation of adult hypothalamic neurogenesis by the photoperiod

Professor Martine Migaud - *INRA-CNRS-Université François Rabelais de Tours, France*

Adult neurogenesis is recognized as the process consisting in the production of new neurons from adult neural stem cells. The hypothalamus, a structure critically involved in the control of neuroendocrine functions, ranging from reproduction, to energy intake/expenditure balance, has recently been shown to host adult neural stem cells within a neurogenic niche. In the ependymal lining of the third ventricle, tanycytes act as the neural stem cells supporting this continuous neurogenesis process. In sheep, a large long living mammalian model, we have recently shown that the hypothalamic neurogenic niche harbours adult neural stem cells (NSCs), the tanycytes capable of generating new neurons and glial cells. In this seasonal species, the function of reproduction is characterized by the alternation of two periods, a period of sexual activity during the short days of autumn and winter followed by a period of sexual rest during the long days of spring and summer. We have shown a seasonal peak in hypothalamic cell proliferation rates occurring around 55 days after the onset of the sexual activity period, concomitant to an increase in the expression of doublecortin, a marker expressed in young migrating neurons, indicating a simultaneous enhancement of the rate of neurogenesis. We provide evidence that this peak of neurogenesis is pineal dependent, suggesting a regulatory role for melatonin in this process. Furthermore, the disruption of hypothalamic neurogenesis following the administration of the antimitotic cytosine-b-D-arabinofuranoside (Ara-C) leads to an alteration of the timing of reproduction. Our results suggest that the photoperiod-regulated hypothalamic neurogenesis plays a role in seasonal reproductive physiology.

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Symposium 5 – Disorders of motivation in brain conditions

Theme: Attention, motivation, behaviour

5.01. Fractionating impulsivity: implications for brain disorders

Professor Trevor Robbins - *University of Cambridge, UK*

The construct of impulsivity is considered within a neuropsychological and neuroscientific theoretical framework that considers different aspects of cognitive control, as well as its possible hierarchical organisation. One neural system, including the medial prefrontal cortex and nucleus accumbens mediates 'waiting' impulsivity, including premature responding in the rodent 5-choice serial reaction time task and temporal reward discounting, with dopaminergic, serotoninergic and noradrenergic modulatory influences. A second system including the dorsal striatum and associated circuitry including the inferior frontal cortex mediates inhibitory control in such tasks as the stop-signal reaction time task and is also modulated by monoaminergic systems. Translational applications of these findings, through the use of tasks with common requirements in rodents and humans and similar effects on task performance of neuropharmacological agents, are identified with respect to human drug addiction, attention deficit/hyperactivity disorder and Parkinson's disease.

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5.02. Multidimensional apathy in neurodegeneration

Dr Ratko Radakovic - *University of Edinburgh, UK*

Apathy is a form of demotivation and is a symptom observed in neurodegenerative disease, frequently reported in dementia, Parkinson's disease and motor neurone disease. It has been linked to cognitive decline, faster disease progression, shorter survival and impairment in daily living in these diseases. There are many issues in the assessment of apathy, examples being the potential overlap with depression and confound of detection due to motor disability. Furthermore, apathy is often measured as a one dimensional construct, summarised as a unitary score, but is in fact multidimensional. This has been observed at descriptive, diagnostic, psychometric and neurobiological levels although there is a lack of consensus on the type and quantity of the dimensions of apathy. Conceptualising apathy as a multidimensional construct has clear research and clinical advantages, allowing for exploration of specific apathy profiles in disease. In our work we firstly developed a new multidimensional apathy tool, suitable for use in people with neurodegenerative diseases. The Dimensional Apathy Scale (DAS) was designed to assess the triadic subtyping of apathy, independent of motor disability. Here we present profiles of apathy in different neurodegenerative diseases, both through patient-control and inter-patient group comparisons, as well as clinical and descriptive associations within these apathy profiles. Further to this we explore cognitive functioning, in the form of executive and emotional cognitive dysfunction, associations with apathy subtypes in motor neurone disease. The impact and possible application of these findings is discussed as a part of research and potential compensatory strategies or interventions. Overarching implications of characterising apathy profiles are presented, as well as the potential benefits of deep subtyping of demotivation.

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5.03. Reward processing in psychiatric disorders

Dr Ciara McCabe - *University of Reading, UK*

It's been suggested that traditional diagnostic boundaries are not entirely useful for capturing the fundamental underlying mechanisms of psychiatric dysfunction (Insel et al., 2010). Rather, examining clinical symptoms as a continuum across symptom severity ranges may be more useful for identifying neurobiological signatures and risk markers. In our study we examine Anhedonia, this is the loss of interest and pleasure when depressed and is both a key symptom of depression and suggested as a possible biomarker of risk for depression (Argyropoulos and Nutt, 2013). We examined how anhedonia, as a continuous measure in adolescents with symptoms of depression, might be related to neural reward function.

Methods: We examined 84 adolescents with high and low depression scores on the Mood and Feeling Questionnaire and the Beck Depression Inventory. 43 adolescents had depressive symptoms and 27 of these clinical depression. Our functional MRI task examined an anticipatory phase (pleasant or unpleasant cue), an effort phase (button presses to achieve a pleasant taste or to avoid an unpleasant taste) and a consummatory phase (pleasant or unpleasant tastes).

Results: Adolescents with depression scores had significantly higher anhedonia scores than those with low depression scores. We also found a significant positive correlation between the scores on the Temporal Experience of Pleasure Scale (TEPS), anticipatory (r=.254, p=.02) and consummatory (r=.263, p=.016) subscales and the brain activation in the ventral striatum for chocolate cue in all subjects. Also, the ventral striatal activation during the chocolate cue correlated with the TEPS consummatory scale in subjects with depressive symptoms (r=.357, p=.019) and those with clinical depression (r=.583, p=.001) sub groups.

Conclusion: Taken together we show that as the experience of pleasure decreased so did the brain activation in the ventral striatum across all subjects. Furthermore we show that this decreased activity is more pronounced in those with depression symptoms and clinical depression. This data supports the utility of neural reward function as a continuous measure underlying the experience of pleasure, that can cut across diagnostic boundaries.

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5.04. Reward and effort-based decision making in health and disease

Professor Masud Husain - *University of Oxford, UK*

What makes us act? Why do we do the things we do? Motivation to pursue goals varies enormously across healthy people. It can be pathologically reduced in patients with brain disorders where it is recognized as a variety of syndromes, including apathy.

We have focused on how apathy relates to the way in which people evaluate rewards for the effort required to obtain them. In healthy people, behavioral apathy (reduced motivation to make act) is associated with increased effort sensitivity. Social apathy is correlated with how much people are willing to invest effort for others compared to themselves. Functional imaging reveals greater recruitment of medial frontal and basal ganglia regions in people who are more behaviourally apathetic, suggesting they might encounter greater brain costs in making effort-based decisions for reward.

Recent work has revealed that rewards can incentivise behaviour by simultaneously increasing movement velocity and improving response precision, thereby breaking the classical speed-accuracy trade-off. We have devised a model to explain these effects by considering the possibility that exerting control to improve response precision might itself come at a cost – a cost to attenuate intrinsic neural noise. Application of a noise-reduction cost to optimal motor control is able to predict empirical findings which show that reward can increase both velocity and accuracy, as well as reduce reaction times and errors.

In patents with Parkinson's disease (PD), a condition associated with dopamine depletion and frequently behavioural apathy we observed reduced reward sensitivity in both speed and accuracy, consistent in our model with higher noise control costs. The pattern of reduced reward sensitivity in PD might be accounted for by a higher cost for controlling noise.

Sensitivity to upcoming rewards is blunted in PD patients who suffer from pathological apathy, but this can be improved on dopaminergic medication. Similarly, on reward for effort-based decision-making tasks or foraging paradigms, patients' choices are modulated by dopamine. These findings suggest that effort-based decision making for rewards provides insight into normal and pathological motivation states in humans.

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Symposium 6 – Epigenetics: causes and consequences in neurological disorders

Theme: Genetics and epigenetics

6.01. The molecular basis of Rett syndrome

Professor Adrian Bird - *University of Edinburgh, UK*

Autism is genetically complex, but several conditions within the autistic spectrum have simple genetic causes. Because of their known origin, single gene disorders of this kind are more straightforward to understand and may hold lessons that apply broadly. An example is Rett syndrome, a profound neurological disorder that almost exclusively results from mutations in the MECP2 gene. Duplication of the MECP2 gene also leads to a distinct autism spectrum disorder. The MeCP2 protein binds to sites on DNA that are chemically altered by DNA methylation and appears to interpret this "epigenetic" mark to affect gene expression. Both the spectrum of mutations causing Rett syndrome and the biochemical and genetic analysis of MeCP2 function support the view that

the primary function of this protein is to inhibit transcription in a DNA methylation-dependent manner. Why should loss of this function affect the brain? Are the resulting defects reversible? What are the prospects for therapy? Current research that aims to address these questions will be presented.

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6.02. Epigenetic studies in Alzheimer's disease

Dr Katie Lunnon, *University of Exeter, UK*

Increasing knowledge about the complexity of the genome has implicated an important role for epigenetic variation in human health and disease. Recent methodological advances mean that epigenome-wide association studies (EWAS) have now been undertaken in a number complex disease phenotypes including Alzheimer's disease. Epigenetic epidemiology is a relatively new endeavor, however, and there are important considerations regarding study design, tissue-type, analysis strategy and data interpretation. Here we describe our recent systematic EWAS and subsequent meta-analyses of DNA methylation and DNA hydroxymethylation in AD. Our studies provide compelling evidence for an association between epigenomic dysfunction and AD-related neuropathology

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6.03. Stability of DNA modifications in Fragile X syndrome and Parkinson's Disease

Dr Reinhard Stöger - *University of Nottingham, UK*

Epigenetic inheritance and the stability of gene expression states often involves modification of DNA. A central question in epigenetics concerns the mechanisms by which a locus maintains, or changes, its epigenetic state. We developed ''hairpin-bisulfite PCR'' to analyse the symmetry – and stability - of cytosine modification events between the complementary strands of individual DNA molecules and used this method to study the FMR1 promoter. Dense methylation at the FMR1 promoter and long-term gene silencing are a common molecular epigenetic signature of Fragile-X syndrome (FXS), the most common form of X-linked intellectual and developmental disability. We used hairpin bisulfite data and applied a new metric, the Ratio of Concordance Preference (RCP) (1), to quantify and compare epigenetic flexibility and stability in a differentiated FXS cell line and induced pluripotent stem cells (iPS) derived from this FXS cell line. The implications for possible epigenetic reprogramming of the FMR1 locus will be discussed. In contrast to FXS, which is characterised by an altered epigenetic state at a single genomic locus, we find evidence that genome-wide epigenetic changes take place in the cerebellum of individuals with Parkinson's Disease (PD). Levels of 5-hydroxymethylcytosine (5hmC), an oxidation product of 5-methylcytosine (5mC) are significantly higher ($p < 0.001$) in cerebellar DNA of both male and female PD individuals compared with age-matched controls (2). The distinct epigenetic profile identified in PD patients raises the question whether this reflects a compensatory role of the cerebellum, or if elevated 5hmC levels are associated with a primary pathophysiological change of PD. We are currently exploring factors that influence the levels of different DNA modifications in this chronic and progressive neurodegenerative disorder.

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2. Stöger R, Scaife PJ, Shephard F, & Chakrabarti L (2016) Elevated 5hmC levels characterize DNA of the cerebellum in Parkinson's disease. npj Parkinson's disease (in press).

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6.04. The role of genomic imprinting in neurological disorders

Professor Rebecca Oakey - *King's College London, UK*

Genomic imprinting refers to the parent-of-origin-specific transcription of a subset of genes controlled by epigenetic mechanisms. Imprinted genes are good models for studying epigenetic mechanisms of gene regulation because the active and silent alleles are

present in the same cell. Imprinted genes are generally co-ordinately regulated in groups by specialised CpG islands termed germline differentially methylated regions which are further connected to imprinting networks across the genome (Patten et al 2015). In terms of function, genomic imprinting is essential for embryonic and foetal development and growth which include roles in placental function and nutrient transfer from mother to offspring. In addition to diverse roles in physiology, it is increasingly acknowledged that imprinted genes influence postnatal functions such as suckling, energy homoestasis and adult behaviour (Wilkinson 2007). It is not therefore surprising that imprinted genes are expressed in the brain and a large number of genome-wide studies have tried to estimate the numbers and pin-point the expression profiles of imprinted genes in the mammalian brain. These studies have been designed to identify parent-or-origin specific and tissue (brain) specific expression with a view to deciphering the contributions of this unusual category of genes to neurological function. Indeed, some brain regions have been identified as ''hot spots'' for genes with parent of-origin-specific expression bias (reviewed in Dent & Isles, 2014). Imprinted genes are associated with neurological disorders and psychiatric illnesses including the classic examples of the human imprinting disorders on 15q11-13, namely Prader-Willi syndrome and Angelman's syndrome. Mouse models have also provided a way to identify the roles of many individual imprinted genes in specific behavioural phenotypes. It has been estimated that of the well-characterised imprinted genes, up to half are expressed in brain and a variety of detailed molecular studies have centred around this important tissue-specific expression. Here we focus on one family of imprinted genes, the imprinted retrogenes, which share the characteristics of exclusive paternal expression, location within the intron of a host gene and derivation from the X-chromosome.

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Symposium 7 – Retrosplenial cortex – a gateway to episodic memories?

Theme: Learning and memory

7.01. Primate retrosplenial cortex: defining its contribution to learning and memory

Dr Anna Mitchell - *University of Oxford, UK*

Primate retrosplenial cortex remains a puzzling cortical brain region. It is one of the earliest brain areas to show hypometabolism in mild cognitive impairment and Alzheimer's disease. While in healthy humans, a plethora of cognitive tasks performed during magnetic resonance imaging, particularly those with a spatial or episodic memory component, produce prominent activation of retrosplenial cortex. Yet still very little is known about its functioning. In my talk, I will present the effects on behavioural and cognitive performance in macaque monkeys after selective, bilateral lesions to the retrosplenial cortex. Retrosplenial cortex damage impaired the ability of monkeys to readily retain object-in-place reward associations learnt prior to brain injury. In contrast, learning new object-in-place reward associations remained relatively intact after retrosplenial cortex damage, although the monkeys showed impaired retention of this initial learning after a 24 hours delay only (Buckley and Mitchell, 2016. Retrosplenial Cortical Contributions to Anterograde and Retrograde Memory in the Monkey. Cerebral Cortex: 26(6): 2905-18). In addition, I will present the structural brain changes, recorded using anaesthetized magnetic resonance imaging, in these same monkeys with bilateral retrosplenial cortex damage. A deformation-based analysis (Sallet J et al. 2011. Social network size affects neural circuits in macaques. Science 334: 697-700) was performed to test for areas of reduced grey matter in the five lesioned monkeys compared to a group of matched control animals.

This work was supported by a UK Medical Research Council Career Development Award - G0800329 to Dr Anna S Mitchell. Dr Mitchell is currently supported by a Wellcome Trust Senior Research Fellowship in Basic Biomedical Science.

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7.02. Retrosplenial cortex: on the outskirts of the spatial memory map

Dr Rafal Czajkowski - *Nencki Institute of Experimental Biology, Poland*

The ability to remember the external environment and to utilize this knowledge is one of the most fascinating adaptive features in the animal kingdom. The development of such capability is related to complexity of brain structure and function. In mammals the central structure involved in spatial memory is the hippocampus. It is responsible for indexing and retrieval of a coherent spatial representation (cognitive map). The entorhinal cortex is anatomically positioned as a gateway to the hippocampal formation. It gathers information from other brain areas and feeds it to hippocampus. It also receives the output of hippocampal processing. One of the less explored elements of this network is retrosplenial cortex (RSC). It harbors head direction cells and damage to this structure impairs spatial navigation based on environmental cues. It is unclear whether this structure encodes or stores the spatial

information. We used a reporter mouse line, in which the expression of GFP was under the control of the c-Fos promoter, and time-lapse two-photon in vivo imaging to monitor neuronal activation triggered by spatial learning. We uncovered a repetitive pattern of Fos activation in RSC. Additionally, we showed that temporary RSC inactivation disrupts spatial memory. Also, overexpressing the transcription factor CREB in the RSC results in spatial memory enhancement. Importantly, silencing the CREB-expressing neurons occludes this effect. These results indicated that RSC engages in formation and storage of memory traces for spatial information. Since RSC projects to the deep layers of MEC, we next tested the functionality of this connection. We applied an optogenetic approach combined with whole cell intracellular recording. RSC fibers and their terminals in MEC were stimulated with brief laser pulses. This protocol revealed a number of hot spots where EPSPs were evoked in recorded layer V cells. Interestingly, these connections underwent spike timing-dependent plasticity. These results confirm that RSC input can directly affect the function of principal cells in MEC LV.

Czajkowski R et al. (2014) Proc. Natl. Acad. Sci. 111:8661-6.
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7.03. Navigating over complex terrain

Professor Kate Jeffery - *UCL, UK*

How the brain collects and organises spatial information is a critical and not-yet-answered question. Study of the neural encoding of space has revealed several classes of neurons that handle different kinds of spatial information including direction, distance and place. However, experiments to study the properties of these neurons have mostly been conducted in simple, flat environments, whereas the real world is complex and three-dimensional. This talk will introduce some of the complexities introduced by complex terrain, and present neuronal data that shed light on how such environmental complexity may be processed.

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7.04. Retrosplenial cortex and stimulus control: investigating non-spatial functions of the rodent retrosplenial cortex

Dr Andrew Nelson - *University of Cardiff, UK*

Given its dense interconnections with the hippocampus and anterior thalamic nuclei, research into the functions of the rodent retrosplenial cortex (areas 29, 30) has understandably focused on its role in spatial learning and memory. However, the retrosplenial cortex also receives sensory inputs from both visual and parietal areas and shares dense connections with the frontal cortex. A consideration of these other connections points to an additional role in cognition beyond the spatial domain. To examine systematically an array of non-spatial functions that may reflect its multimodal inputs and interconnections with frontal cortex, we tested the impact of retrosplenial damage on a series of non-spatial tasks that have either been typically linked to frontal function or tax the integration of different classes of sensory information. Rats with excitotoxic lesions in the retrosplenial cortex were impaired on tests of object recency memory, a rodent analogue of the Stroop task, cross-modal recognition memory and sensory preconditioning. However, other tasks typically associated with frontal cortex including response inhibition, rule switching and attentional set shifting were all unaffected by retrosplenial damage. Taken together, these results extend the class of stimuli that depend on retrosplenial processing, thereby highlighting the parallel importance of the retrosplenial cortex for both non-spatial, as well as spatial, stimuli. To unify these apparently disparate cognitive functions, it is proposed that these sub-roles are linked by the overarching property of stimulus control: that this regions enables the translation of information between different frames of reference with comparable roles for both spatial and non-spatial problems.

This work was supported by the BBSRC.

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Symposium 8 – Treating anxiety – the role of benzodiazepines and beyond

Theme: Psychiatry and mental health

8.01. Neuronal pathways and molecular targets for modulation of anxiety

Professor Esa Korpi - *University of Helsinki, Finland*

Feelings of anxiety and fear, present at varying intensities in anxiety disorders and depression, are mediated by a variety of brain pathways, often conditioned to signals from external environment and internal thoughts. The main anxiety mechanisms are associated with the extended amygdala, septo-hippocampal system and the prefrontal cortex. Autonomic responses are mediated via hypothalamic and brainstem pathways activating the sympathetic nervous system. There is a genetic basis for susceptibility to anxiety disorders in humans and animal models, but the mechanisms are poorly characterized. Furthermore, early life experiences may strongly affect adult anxiety-like behaviors. Traditionally, anxiety has been damped by alcohol and sedative drugs of abuse, sometimes leading to addiction. Allosteric benzodiazepine receptors at the GABA type A receptors show great heterogeneity that has been used in developing subtype-selective anxiolytics, but so far they have failed in early clinical trials. Another class of rapidly acting anxiolytics is the gabapentinoids, which bind to an auxiliary subunit of voltage-gated calcium channels and downregulate presynaptic channel trafficking leading to reduced glutamate release. Down-regulation of glutamate transmission is thus considered as a possible target for rapid anxiolysis. These treatments may lead to tolerance. Novel findings on mitochondrial functions have recently emerged, with the peripheral benzodiazepine receptor (known as the translocator protein, TSPO) that regulates neurosteroid synthesis, being actively pursued. The present first line treatment of anxiety starts with antidepressants, based on the idea of allowing relearning/neuroplasticity of synaptic contacts in critical points of the pathways mediating abnormal conditioned anxiety. These drugs, however, are not acutely efficient. Modulation of anxiety has been achieved in some models by activation/inhibition of specific brain pathways, which holds the promise of the better understanding of the molecular/cellular pathways for increased susceptibility and resilience, leading to ways to alleviate anxiety disorders.

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8.02. Past, current and future drug treatments for anxiety

Dr Gerry Dawson - *P1Vital, Oxford, UK*

In the past 15-20 years, new technologies and techniques to probe brain function have been developed and a wealth of new drug targets aimed at improving the treatment of anxiety and other psychiatric disorders have been proposed. Often, new compounds show great promise in animal studies, but then fail in early clinical trials for lack of efficacy. A case in point is the development of subtype selective GABA-A receptor agonists that had anxiolytic-like effects in animals and were also free of sedative and other side effects. However, in healthy human volunteers at doses that resulted in low receptor occupancy profoundly sedative effects were observed. As a result new treatments for anxiety and other psychiatric disorders have declined significantly as the effects of compounds in animals are not always predictive of effects in human clinical trials. Thus the classical route for drug development from animal to humans failed in this case. One mitigating strategy is to conduct human experimental and translational medicine studies that focus on detecting the efficacy of new compounds before large patient trials are initiated. Two types of study have evolved. The first employs healthy volunteers performing tasks that activate specific brain circuits that may be modulated by compounds of interest and observed by modern brain imaging techniques. The second has a surrogate patient population with mild symptoms or a subset of symptoms, present in patient populations that may respond to the compound of interest and where symptom reduction may be observed. Such studies provide valuable information on the location and mechanism of existing and new drug treatments. The resulting data demonstrate the value of relatively small studies with a high degree of replication and reproducibility. They facilitate early and even late stage, treatment development by elucidating the mechanisms of action of drugs or classes of drugs and the brain systems they modulate. In some cases the biomarkers emerging from such studies can also be deployed in primary care to aid, for example, the diagnosis and management of the treatment of anxiety and depression.

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8.03. Targeting cognitive control to reduce anxiety vulnerability: implications for treatment efficacy

Professor Nazanin Derakhshan - *Birkbeck, University of London, UK*

The modulating role of cognitive control in anxiety treatment and prevention is becoming increasingly important with vital implications in clinical and educational sciences. Accumulative evidence from neurocognitive training interventions aiming to increase processing efficiency in vulnerable populations support theoretical predictions that the adaptive and systematic exercise of cognitive control processes should reduce anxiety and depressive vulnerability. In this talk I will present new evidence showing that adaptive cognitive training can reduce anxiety and depression in a variety of vulnerable populations suffering high anxiety in clinically related (e.g., survivors of breast cancer) and educational settings (e.g., anxious adolescents). I will also discuss evidence to show how such neurocognitive training protocols can aid in the longer term efficacy of traditional therapies such as mindfulness.

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8.04. Deconstructing the molecular pathways to benzodiazepine tolerance - where do we stand and where do we go?

Dr Jasmina Jovanovic - *UCL, UK*

Benzodiazepines facilitate the inhibitory actions of GABA by binding to an allosteric binding site on the GABAA receptor. This activity underpins distinctly potent and rapid anxiolytic, anticonvulsant, myorelaxant and hypnotic effects of benzodiazepines in patients. However, the clinical use of benzodiazepines leads to a gradual development of tolerance to their pharmacological effects and physical dependence.

GABAA receptors represent a large and diverse family of GABA-gated chloride/bicarbonate channels, which mediate the majority of the fast inhibitory neurotransmission in the brain. To date, the cellular and molecular changes in this neuronal system caused by sustained exposure to benzodiazepines remain poorly characterised. Here we report that prolonged GABAA receptor activation by diazepam, the most widely used benzodiazepine in clinic, led to a gradual disruption of functional inhibitory GABAergic synapses, which was correlated with a pronounced decrease in the number and size of synaptic GABAA receptor clusters as well as in their association with the presynaptic GABA-releasing terminals. Moreover, a concomitant time- and dose-dependent decrease in the overall cell surface expression of GABAA receptors in response to diazepam was detected and shown to be mediated by the dynamin-dependent internalisation. In the presence of Ro 15-4513, a benzodiazepine site antagonist, bicuculline, a GABA site antagonist, or picrotoxin, a GABAA channel blocker, both the loss of synapses and endocytosis of GABAA receptors were abolished, indicating that the receptor activation is integral to the mechanisms triggering these processes. Further characterisation has revealed the critical role of calcium released from the intracellular calcium stores and the calcium/calmodulin-dependent phosphatase calcineurin in regulating the internalisation of GABAA receptors and disruption of GABAergic synapses. Thus, sustained activation of GABAA receptors by benzodiazepines has a paradoxically opposite effect on the stability of GABAergic inhibitory synapses. It remains to be established whether these synaptic changes represent the missing piece in the puzzle of mechanisms underlying benzodiazepine tolerance in patients.

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Symposium 9 – Towards disease modifying drugs for neurodegeneration: connecting learnings from genetics, molecular and pathology studies

Theme: Neurodegenerative disorders and ageing

9.01. Using novel genetic approaches to probe the causes of neurodegenerative disease

Dr Rita Guerreiro - *UCL, UK*

The development of different whole genome genotyping and sequencing platforms has enabled an ever increasing number of genetic discoveries in neurodegenerative diseases. We are now able to determine variation and structure at a genome-wide level, with base-pair resolution and to assess its impact on phenotypes in an unprecedented manner. For example, the application of whole exome sequencing to the study of dementias has allowed the identification of novel causative genes in mendelian forms of frontotemporal dementia (e.g.: CHCHD10 p.S59L mutation as the cause of FTD-ALS (Bannwarth et al. 2014)), rare variants decreasing and increasing the risk for Alzheimer's disease (e.g.: APP p.A673T and TREM2 p.R47H, respectively (Jonsson et al. 2012; Guerreiro et al. 2013)) and a series of pleiotropic events (e.g.: ATP13A2 mutations as the cause of Kufor-Rakeb syndrome and of Neuronal ceroid lipofuscinosis with juvenile onset (Ramirez et al. 2006)(Bras et al. 2012)).

In this talk I will review the most recent findings established by the application of these platforms to the study of familial and sporadic forms of different neurodegenerative conditions. I will describe the main approaches currently being used and discuss how genetic results can be used towards the development of therapeutic agents and the improvement of clinical trials.

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9.02. Propagation of tauopathy: mechanisms and therapeutic opportunities

Professor Karen Duff - *Columbia University, USA*

The spread of tau pathology in Alzheimer’s disease is predictable and consistent, and the route taken suggests that the pathology follows neuroanatomical connections. We have modeled the spread of tauopathy from regions of initial vulnerability in transgenic mice (Liu et. al. PLoS One 7(2) 2012) and have demonstrated that the exacerbation and spread of pathology to secondary areas correlates with degeneration and cognitive impairment similar to that seen in human AD (Fu et. al. 2016). In vitro studies have shown that tau can pass from neuron to neuron, via the extracellular space (Wu et. al. 2016) suggesting that pathological forms of tau can be propagated between brain regions following the release of tau from donor neurons, and uptake and templating by recipient neuron. Enhanced neuronal activity can accelerate tau transfer between neurons in vitro, and can accelerate tauopathy progression in vivo (Wu et. al. 2016). Cellular clearance mechanisms are impacted by the accumulation of pathological tau in neurons (Myeku et. al. 2016), and deficits in these pathways may explain how pathology worsens and spreads. Therapeutics aiming to boost clearance pathways may delay or halt disease progression and be of clinical benefit.

Fu et. al. PLoS One 11(7) 2016
Wu et. al. Nat. Neuro. 19(8) 2016
Myeku et. al. Nat. Med. 22(1) 2016

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9.03. Alpha-synuclein trafficking as a rational mechanism for therapies in Parkinson’s Disease

Professor George Tofaris - *University of Oxford, UK*

Parkinson’s disease is the second most common neurodegenerative disorder, with only partial symptomatic therapy and no mechanism-based therapies. The accumulation of α-synuclein is causatively linked to the sporadic form of the disease which accounts for 95% of cases. The pathology is due to a gain of toxic function of misfolded α-synuclein conformers, which can template the aggregation of soluble monomers and lead to cellular dysfunction as well as transcellular propagation. We have used a multifaceted approach including neuropathological studies, cellular and biochemical assessment of mechanisms and modeling of proteotoxicity in Drosophila to understand the molecular underpinnings of ubiquitin signalling in α-synuclein biology. Our work has unraveled a pathway by which the E3 ligase NEDD4 and deubiquitinase USP8 target α-synuclein to the lysosome and demonstrated the relevance of these enzymes in models of α-synuclein toxicity. These findings suggest a central role for endosomal/lysosomal

trafficking in α-synucleinopathies, which will be discussed in the context of genetics, prion-like mechanisms and therapeutic potential.

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9.04. Industry approaches to therapeutic development for Alzheimer's Disease

Michael Hutton - *Eli Lilly & Co. Ltd., UK*

Alzheimer's Disease is the most common cause of dementia that affects an estimated 10.5M patients in Europe alone. This represents a major and increasing challenge to the sustainability of national healthcare systems in addition to the impact on patients and their caregivers. However at present only symptomatic treatments that provide limited cognitive benefit are available and there are currently no disease modifying treatments that can slow or halt clinical progression by targeting the underlying mechanism of the disease. The predominant hypothesis proposed to explain the pathogenesis of the disease focuses on the early accumulation of toxic assemblies of Aβ that are proposed to drive the development of other downstream pathological changes including Neurofibrillary (tau) tangles, synaptic and neuronal loss. However the recent failure of multiple potential drugs (including bapineuzumab, solanezumab and verubecestat) designed to target the amyloid pathway has led many to question the role of Aβ in the disease and its potential as a route for therapeutic intervention.

This presentation will review the potential reasons for the failure of these amyloid-based therapies and examine the remaining molecules designed to target the amyloid pathway that are still in clinical development. In addition to amyloid-based approaches, a number of other targets are now being explored by Pharma, Biotech and Academic teams, as a source of potential disease modifying treatments with particular emphasis on tau and neuroinflammation. The current status of these other approaches will also be discussed.

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