Special event 5 – Breaking neuroscience

SpE5.01. The insular cortex and impulse control

Dr David Belin - *University of Cambridge, UK*

Increasing evidence suggests that neurobiological alterations within the cortico-striatal circuitry contribute to impulsivity and compulsivity, which are core mechanisms underlying psychiatric disorders such as drug addiction or Obsessive Compulsive Disorder. Studies have hitherto focused on the role of the prefrontal and orbitofrontal cortices and their functional interaction with the ventral striatum in the regulation of impulse control and the association pathophysiology of impulsive/compulsive disorders. However, we speculate that beyond deficits in prefrontal cortex dependent top-down executive inhibitory mechanisms, maladaptive impulse control relies on a failure to integrate internal states which leads to an altered interaction between subjective feelings and executive function, as suggested by the somatic marker hypothesis. At the neurobiological level, the anterior insula, which function is altered in OCD, is suggested to gate somatosensory information. Nevertheless, little is known about its role in impulsivity and compulsivity.
We will review recent evidence that the anterior insula is a gateway from impulses to maladaptive actions, contributing not only to inter-individual differences in decision making and impulsivity but also to the development of compulsive behaviours and loss of control over drug intake.
This will offer avenues for a shift in the theoretical framework of impulse control whereby the qualitative and quantitative nature of the impulse, speculated here to be dependent on the insula, should be considered to play as much a role in impulse control as the executive system dependent on the prefrontal cortex.

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SpE5.02. Microglial immune surveillance powered by potassium channels

Dr Christian Madry – *UCL, UK*

Microglia, the brain's immune cells, continually extend and retract processes to survey the brain. This surveillance may be needed to prune redundant or damaged synapses during development or pathology, to modulate neuronal activity and to detect pathogenic agents, but its mechanism is obscure. To examine the signalling regulating microglial process movement, we imaged and whole-cell clamped microglia *in situ* in brain slices and *in vivo*. Tissue damage or ATP application led to membrane hyperpolarization mediated by a $P2Y_{12}$ receptor-linked ion channel that we identify as the anaesthetic-sensitive two-pore domain K^+ channel THIK-1, and evoked process outgrowth towards the ATP source. Blocking $P2Y_{12}$ receptors prevented process outgrowth in response to ATP released by tissue damage but did not affect the membrane potential or surveillance of the brain by microglia. In contrast, blocking tonic activity of THIK-1 with K^+ channel inhibitors, gene knockout or gaseous anaesthetics, or locally raising $[K^+]_o$, depolarised microglia and decreased microglial ramification and surveillance of the brain. Blocking THIK-1 activity also inhibited interleukin-1brelease evoked by ATP/lipopolysaccharide-evoked microglial activation. Thus, regulation of the microglial membrane potential by THIK-1 channels (which are not expressed by the cultured microglia often used to assess brain immune function) controls immune surveillance of the brain and immune effector release, suggesting that modulation of THIK-1 channels could be used to alter these functions therapeutically. The inhibitory effect of gaseous anaesthetics on THIK-1 implies that brain immune function may be suppressed in clinical situations using these agents.

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SpE5.03. Is glutamate release required for synaptic plasticity?

Dr Zahid Padamsey - *University of Oxford, UK*

It is widely assumed that the neurotransmitter glutamate is required for long-term synaptic plasticity at excitatory synapses. Accordingly, a synapse must release glutamate in order to become potentiated. This view is consistent with the traditional framework of long-term potentiation (LTP), in which postsynaptic NMDA receptor (NMDAR) signaling is necessary to drive changes in synaptic efficacy.

At hippocampal CA3-CA1 synapses we re-examine the role of glutamate in synaptic plasticity. Remarkably, we find that synapses undergo LTP in the absence of glutamatergic signaling. This form of LTP is 1) Hebbian, in that it requires presynaptic activity to coincide with postsynaptic spiking, 2) site specific, in that it does not spread to inactive synapses, and 3) expressed presynaptically, as a change in the propensity of synapses to release glutamate.
Mechanistically, this form of LTP requires postsynaptic depolarisation to drive the release of nitric oxide from neuronal dendrites, and in a manner that depends on postsynaptic L-type voltage-gated Ca2+ channel activation; importantly, nitric oxide release does not directly depend on glutamate release or postsynaptic NMDAR signaling. Moreover, we find that glutamate release only serves to inhibit the induction of this form of LTP, and instead drives presynaptic long-term depression (LTD) by acting on presynaptic NMDARs.
Our findings reveal a novel plasticity rule for central synapses, one in which glutamate release is inhibitory and unnecessary for the long-term potentiation of presynaptic function.

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SpE5.04. Sustained correction of associative learning deficits following brief, early treatment in a rat model of Fragile X Syndrome

Antonis Asiminas – *University of Edinburgh, UK*

Fragile X syndrome (FXS), is the leading inherited cause of intellectual disability and autism, affecting hundreds of thousands of people worldwide. Despite the early emergence of symptoms associated with FXS, it is still not clear whether treatments restricted to early development of brain circuits can permanently prevent impairments in cognitive function. Key to addressing such issues is knowledge of the development trajectory of cognitive abilities in animal models.
In this study, we used a novel rat model of FXS to test the hypothesis that the deficits in associative memory tasks can be prevented by early therapeutic intervention and whether benefits are maintained after termination of the treatment.
We employed a set of behavioural paradigms suitable for repeated testing in the same animals without being confounded by reward-based learning. Juvenile rats were fed either a control or a lovastatin-enriched (100mg/kg) diet between 4 and 9 weeks old and tested in 4 spontaneous object exploration tasks. WT animals treated with lovastatin remained unaffected while KO rats which received lovastatin met normal developmental millstones for all exploration tasks. Furthermore, when the same animals were tested more than 3 months after the end of the treatment showed the same behavioural profile compared to the end of the treatment. This behavioural rescue was corroborated by normalization in basal protein synthesis and synaptic plasticity in prefrontal cortex.
Our results show that not only we can prevent the emergence of cognitive deficits associated with Fragile X Syndrome but also that therapeutic interventions in potentially critical developmental windows can have permanent effects.

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Symposium 32 – Understanding microglial functional heterogeneity in the health and diseased brain

Theme: Neuronal, glial and cellular mechanisms

32.01. Origin and fate of CNS macrophages

Professor Marco Prinz - *University of Freiburg, Germany*

The diseased brain hosts a heterogeneous population of myeloid cells, including parenchymal microglia, perivascular cells, meningeal macrophages and blood-borne monocytes. To date, the different types of brain myeloid cells have been discriminated solely on the basis of their localization, morphology and surface epitope expression. However, recent data suggest that resident microglia may be functionally distinct from bone marrow- or blood-derived phagocytes, which invade the CNS under pathological conditions. During the last few years, research on brain myeloid cells has been markedly changed by the advent of new tools in imaging, genetics and immunology. These methodologies have yielded unexpected results, which challenge the traditional view of

brain macrophages. On the basis of these new studies brain myeloid subtypes can be differentiated with regard to their origin, function and fate in the brain (1,2).

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32.02. Multiple identities of microglia across the adult lifespan

Dr Barry McColl - *University of Edinburgh, UK*

Microglia are the specialised macrophages of the central nervous system (CNS) parenchyma. Like macrophages in all tissues, microglia are key immune sentinels and effectors but also have important homeostatic and housekeeping functions. Phenotypic diversity and plasticity of macrophage populations are increasingly recognised as a basis for enabling these multi-functional and tissue-specific roles (e.g. synaptic organisation in the brain, iron recycling in the spleen). In the brain, little is known about steady-state microglial diversity particularly in the context of the regional functional specialisation of the CNS. We have explored the extent and nature of steady-state microglial regional heterogeneity on a transcriptome-wide scale across the adult lifespan in mice. We have found that microglia have distinct region-dependent transcriptional identities that suggest microglia in some brain regions exist in a more immune-vigilant state, in part through regional differences in the balance between amplifying and inhibitory immunoreceptors. Moreover, our results have shown that microglia age in a regionally variable manner. Divergent ageing trajectories in hippocampal and cerebellar microglia affecting immunoregulatory and environment sensing pathways were notable. Regional diversity may enable microglia to meet location-specific demands of brain tissue but may also underlie region-specific sensitivities to microglial dysregulation and involvement in age-related neurodegenerative disease which often occur in spatially-restricted patterns. In this talk I will discuss some of these concepts and their relevance to modelling and treatment of age-related neurodegenerative disease.

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32.03. Microglial self-renewal and proliferation in health and disease

Dr Diego Gomez-Nicola - *University of Southampton, UK*

Microglial cells are the resident immune cells of the brain and play crucial roles in the regulation of normal and pathological neural functions. Our lab aims at studying the balance of the numbers of microglial cells from development to ageing, to better understand the roles of these cells in the brain, through a multidisciplinary approach using in vivo models, genetic molecular tools and behavioural analysis of brain function. We aim to define how microglial cells control their numbers and phenotype during not only healthy ageing, but also disease. Microglial cells play a key role in the development and maintenance of the inflammatory response characteristic of several neurodegenerative disorders, showing enhanced proliferation and morphological activation. We are using a multidisciplinary approach combining the study of laboratory models of chronic neurodegeneration, including prion disease, Alzheimer's disease (AD) and ALS, with the study of post-mortem samples from patients, to describe the time-course and regulation of microglial proliferation. Our results demonstrate that microglial proliferation is an important feature of the evolution of chronic neurodegenerative disease, with direct implications for understanding the contribution of the CNS innate immune response to disease progression. We have shown that the control of microglial numbers in prion, AD and ALS is regulated by the activation of the Colony Stimulating Factor 1 Receptor (CSF1R). Pharmacological inhibition of CSF1R leads to a diminished proliferation of microglia and the amelioration of the behavioural and neuropathological symptoms of chronic neurodegeneration.

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32.04. Cellular and molecular mechanisms underpinning microglia-driven myelin regeneration

Dr Veronique Miron - *University of Edinburgh, UK*

The prime example of effective regeneration in the central nervous system is that of remyelination, whereby re-enstheathment of axons with myelin restores electrical impulse conduction and trophic/ metabolic support. Remyelination fails in a multitude of neurological disorders, which is considered to contribute to the axonal damage/ loss correlating to clinical decline. The lack of approved therapies promoting remyelination highlights the need to elucidate the underpinning mechanisms. Our previous work showed that efficient remyelination requires dynamic regulation of microglia activation, with a transition from a pro-inflammatory (iNOS+ TNF-alpha+ CD16/32+) to regenerative phenotype (Arg-1+ CD206+ IGF-1+) needed to initiate remyelination. The chronic pro-inflammatory microglia activation commonly observed in neurological disorders suggests an impairment in this transition. However, the cellular and molecular mechanisms regulating the activation of microglia and resolution of inflammation are unknown. Using a combination of ex vivo and in vivo modelling of myelin damage, live imaging of microglia dynamics, and correlation to human CNS pathology, we have unveiled hitherto unrecognized cellular and molecular events that control microglia activation and remyelination. We believe that these reveal novel therapeutic strategies to dampen CNS inflammation-associated pathology and support a regenerative response to reinstate neural health.

This study is funded by a BBSRC-CASE industrial studentship in collaboration with GSK (A.F.L.), an MRC/ MS Society Career Development Award (V.E.M.), and funds from the MRC Centre for Reproductive Health.

All animal studies were ethically reviewed and carried out in accordance with Animals (Scientific Procedures) Act 1986 (and the GSK Policy on the Care, Welfare and Treatment of Animals).

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Symposium 33 – What is special about 'social'?

Theme: Attention, motivation, behaviour

33.01. Sociality from primates to humans

Professor Robin Dunbar - *University of Oxford, UK*

Primates have a distinctive form of sociality that involves bonded relationships that are very different from those found in most other mammals. This involves a dual-process mechanism partly dependent on advanced cognitive abilities (the social brain hypothesis) and partly on the use of social grooming to trigger the endorphin system. Humans have extended both of these so as to allow us to form unusually large and structurally complex social groups (by primate standards). Aside from finding novel behavioural ways of triggering the endorphin system on a larger scale than can be done with grooming (including laughter, singing, feasting), this has involved coordinating the way the five main neuropeptides (endorphins, oxytocin, vasopressin, dopamine and serotonin) interact at different social levels.

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33.02. Developmental perspective on 'what is special about 'social'?'

Professor Mark Johnson - *Birkbeck, University of London, UK*

From birth, typical infants preferentially attend to social stimuli, and this initial bias helps to tune later developing cortical circuity to build the specialized social brain network observed in adults. In adults with autism, the social brain network appears to be differentially impaired, or less specialized. Our research with infants at-risk for autism examines hypotheses about how this 'social

deficit' emerges from early development, and thus sheds light on what is special about 'social'. Our results support the view that domain general factors in early postnatal brain development can differentially effect the emerging social brain.

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33.03. Toward a social psychophysics of face communication

Dr Rachael Jack - *University of Glasgow, UK*

Humans are a highly social species, and are equipped with a powerful tool for social communication---the face. By virtue of the rich variations of the movements, morphology, and complexion of the face, it can elicit multiple social perceptions. Consequently, identifying precisely what face information elicits different social perceptions is a complex empirical challenge that has largely remained beyond the reach of traditional methods. More recently, the emerging field of social psychophysics has developed new methods to address this challenge, with the potential to transfer psychophysical laws of social perception to the digital economy via avatars and social robots. At this exciting juncture, it is timely to review these new methodological developments. Here, I will introduce and review the foundational methodological developments of social psychophysics, present recent work that has advanced understanding of the face as a tool for social communication, and discuss the major challenges that lie ahead.

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33.04. Eye contact and social interaction

Dr Antonia Hamilton - *UCL, UK*

Living creatures (humans, pets) can typically see objects and people in the world, while non-social items cannot. Thus, comprehension of another person's visual world and the feeling of being seen by another may be special to social cognition. Here I present a series of studies examining how being seen changes adults' behaviour (audience effects) and motivation. Current data shows that typical adults, infants and children imitate more when watched, but adults with autism do not. This effect is found in both constrained and naturalistic situations, and is linked to the function of medial prefrontal cortex. Also, typical adults also prefer videos of people making eye contact to videos without eye contact, and this preference is reversed in adults with autism. Together, these studies show that cues about the physical presence of other people and their gaze can have important influences on human behaviour.

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Symposium 34 – MRI at 7 Tesla: new capabilities and insights

Theme: Sensory and motor systems

34.01. Somatosensory plasticity at 7T: fMRI, spectroscopy and behaviour

Dr James Kolasinski - *Cardiff University, UK*

The ordered topography of primary somatosensory cortex (SI) has long served as a model system for studies of both cortical organisation and reorganisation. To date, investigating the fine-grain detail of such cortical maps has largely remained the domain of electrophysiologists working with animal models. However, with recent advances in the spatial resolution of fMRI, afforded by the advent of 7 tesla systems, it is now feasible to resolve the detailed functional architecture of SI at the level of individual human participants.

Here I present the results of a series of studies focused on understanding the organisation and plastic potential of the primary sensory cortices, using 7 tesla mapping of finger somatotopy in human SI as a model system. I will briefly outline the mapping paradigm applied, highlighting the ability to reproducibly map detailed functional organisation at the level of single subjects. I will then move on to discuss two key experiments probing the propensity for short-term and long-term experience-dependent plasticity in cortical topography. A study of short-term plasticity reveals a striking shift in the topographic representations of the fingers after just 24-hours of altered hand use, mirrored by corresponding changes in tactile perceptual acuity. A subsequent study explores the persistence of topographic features in the absence of sensory inputs, using upper-limb amputees and phantom sensations to explore the functional reorganisation of SI. This work reveals latent but preserved representations of the missing fingers in SI, even

decades after amputation. Finally, I will attempt to explain the inter-subject variability observed in fine-grain cortical somatotopy in terms of the underlying neurochemical milieu and explore how this variability maps to individual differences in perceptual acuity.

This range of studies showcases the exciting potential of ultra-high field 7 tesla MRI to address questions previously unfeasible using human neuroimaging.

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34.02. Uncovering the basis of sensory experience using 7T

Dr Andrew Welchman - *University of Cambridge, UK*

How do we see the world around us? Understanding the organization of sensory computations within the visual cortex represents a longstanding challenge that 7T imaging is well placed to address. Here we discuss work that has examined the neural basis of three-dimensional (3D) perception in the human brain using ultra-high field fMRI. We take advantage of the high spatial specificity and image contrast offered by 7 tesla fMRI to test for systematic organization of binocular depth signals across the cortical surface, and at different laminar depths. By parametrically manipulating binocular disparities, and repeating measurements across separate imaging sessions, we have been able to provide three main advances in understanding disparity organization in the human brain. First, we show that disparity preferences are clustered and that this organization persists across imaging sessions. Second, we find differences between the local distribution of voxel responses in early and dorsomedial visual areas, suggesting different cortical organization. Third, using modelling of voxel responses, we show that higher dorsal areas (V3A, V3B/KO) have properties that are characteristic of human depth judgments: a simple model that uses tuning parameters estimated from fMRI data captures known variations in human psychophysical performance. These findings indicate that human dorsal visual cortex contains selective cortical structures for binocular disparity that may support the neural computations that underlie depth perception. This provides a promising foundation from which to use ultra-high field imaging to uncover the fine neural representations responsible for perception.

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34.03. High-resolution MRI of the human visual system - challenges and opportunities at ultra-high field

Dr Ivan Alvarez - *University of Oxford, UK*

The advent of 7T MRI has permitted investigations of human cortical function and organisation previously unavailable with non-invasive imaging techniques. The increase in field strength results in an increased signal-to-noise ratio (SNR) that can be exploited (i) to boost sensitivity to weak neural signals, (ii) to decrease spatial resolution to reveal detailed functional organisation at a macroscopic level and (iii) to improve discriminability of biologically relevant neurochemicals with 1H magnetic resonance spectroscopy.

We present three experiments exploiting the increased SNR to investigate the functional organisation of the visual system. First, we investigated responses to retinotopic stimuli to characterise the population receptive field (pRF) properties of cortical visual areas. The increased SNR at 7T permitted detection of responses to stimuli defined by binocular disparity throughout the visual cortical hierarchy, as well as responses to luminance, contrast and motion-defined stimuli. Comparing pRF sizes for stimuli modulated with binocular disparity against those modulated with monocular cues, pRF sizes were larger for the binocular condition at the first stage of cortical visual processing (V1), a pattern also evident in the ventral visual stream (LOC).

Second, the functional architecture of human visual area V2 was mapped with high-resolution (0.7mm) fMRI, revealing local sensitivity to colour and motion within V2 as predicted by optical imaging in the macaque monkey. Furthermore, this approach demonstrated that these interdigitated patches had spacing comparable to the thin, thick and pale stripe organisation evidenced through histological staining.

Finally, we present work quantifying the relationship between neurotransmitter concentrations and BOLD responses in early visual cortex. Through interleaved acquisition of magnetic resonance spectroscopy and fMRI, we show that concentrations of excitatory glutamate and the BOLD response in V1/V2 vary systematically during brief periods of visual stimulation. This innovation will allow the concurrent study of neural activity and neurochemistry to understand the mechanisms underlying the BOLD signal.

This work was supported by the Medical Research Council, the Wellcome Trust and the Royal Society.

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34.04. Applications of z-spectrum imaging at 7T

Professor Penny Gowland - *University of Nottingham, UK*

The conventional magnetization transfer (MT) experiment can be adapted for so called z-spectrum imaging by varying the off-resonance frequency of the saturation pulse. The z-spectrum demonstrates a number of features including the main magnetization transfer baseline, a so called Nuclear Overhauser (NOE) peak and the Chemical Exchange Saturation Transfer (CEST) peaks. These latter peaks relate to moieties such as amines, amides and glucose and considerable work is still required to separate them adequately. In the brain it seems that NOE relates to myelin and it has been shown that the MT line width depends on orientation.

MT have provided useful surrogate measures of myelination and we have used the increased sensitivity available at 7T to study the anatomical connectome and to link this to the functional connectome We have also used MT to detect grey matter lesions in multiple sclerosis and the effect of such lesions on underlying white matter. We have investigated the use of CEST measures to identify active tumour regions.

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Symposium 35 – What the brain tells us about the mind: lessons from neuropsychiatry

Theme: Psychiatry and mental health

35.01. Disorders of visual imagery

Professor Adam Zeman - *University of Exeter, UK*

For most of us visual imagery is a conspicuous ingredient of the imaginative experience which allows us to escape from the here and now into the past, the future and the worlds conceived by science and art. Neurologists since Charcot have described occasional patients who have lost the ability to summon imagery to the mind's eye as a result of probable or definite brain damage: Farah distinguished deficits due to impairments of visual memory, image inspection and imagery generation (The neurological basis of mental imagery: a componential analysis. Farah, M.J. Cognition 1984;18, 245-272). Psychiatrists have recognised that conditions such as depression and depersonalisation can affect the vividness of imagery. Functional imaging studies have elucidated a network of brain regions involved in visualisation, including both modal and supramodal areas. We recently described a group of people with lifelong absence of the mind's eye, terming this variation in human experience 'aphantasia' (Lives without imagery – congenital aphantasia. Adam Zeman, Michaela Dewar, Sergio Della Sala. Cortex 2015; 73:378-380). This talk will review the clinical and scientific background of disorders of visual imagery, and report on the preliminary results of our analysis of data from several thousand participants whose imagery falls at the extremes of the vividness spectrum. We are grateful to the AHRC for their support for this work through a Science In Culture Innovation Award: see http://medicine.exeter.ac.uk/research/neuroscience/theeyesmind/ for further details of the Eye's Mind Project.

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35.02. Impulse control disorders in Parkinson's disease

Dr Valerie Voon - *University of Cambridge, UK*

Impulse control disorders or behavioural addictions related to dopaminergic medications are common in Parkinson's disease. These behaviours can include pathological gambling, eating, sexual or shopping behaviours. What drives these behaviours? Why does one develop one behaviour and not another? This talk reviews novel developments in understanding the underlying pathophysiology. Recent evidence highlights a role for parkinsonian rodent models in enhancing the reinforcing properties of dopaminergic medications. Converging human and animal data further emphasizes a role for enhanced stimulus-induced dopamine function. Impairments in decisional impulsivity but not motor impulsivity implicates ventral rather than dorsal striatal engagement. Finally, differences as a function of behavioural expression highlight potential differences underlying behavioural addiction subtypes. These behaviours shed light on basic underlying mechanisms linking dopamine and behavioural function.

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35.03. What amnesia tells us about memory functions

Dr Nils Muhlert - *University of Manchester, UK*

Generations of researchers have used the study of people with amnesia to gain insight into the mechanisms of memory. For instance, amnesia following head trauma often affects memory for the recent, as opposed to distant, past, suggesting qualitative differences between these forms of memory. Similarly, accelerated rates of forgetting of newly learned information has been reported following damage to limbic brain structures, providing potential insight into neurobiological mechanisms. More recently, a series of reports has focussed on forgetting rates in people with temporal lobe epilepsy. These paint a picture of both fast and slow stabilisation of long-term memories that may, in part, be dissociably affected. In this talk, I consider whether studies of people with amnesia converge in demonstrating a separation of early and late long-term memory, and what this might suggest for normal memory function.

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35.04. Brain control – scientific and clinical developments and ethical implications

Professor David Linden - *University of Cardiff, UK*

Neuroscience has a long history of attempts to control the brain, which has important clinical and philosophical implications. I will discuss therapeutic techniques based on brain stimulation that aim to control or modulate specific circuits of the brain in order to improve the symptoms of neurological or psychiatric diseases. I will explain that these techniques have considerable therapeutic potential but also raise important issues about their theoretical foundation (for example regarding the function/ dysfunction of these circuits in disease), potential side effects, changes to patients' personality and other ethical questions. I will also argue that brain modulation techniques are not confined to external (invasive or non-invasive) brain stimulation. Learning to modulate one's own brain activity through neurofeedback training could be another way of targeting circuits that are relevant to the disease process or might compensate for an underlying dysfunction. I will summarise the theoretical foundation and clinical evidence for these different neuro-modulation approaches with a particular focus on psychiatric applications and discuss how interaction between basic and clinical neuroscience can boost the further development of this field.

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Symposium 36 – Early life stress: consequences for neurodevelopment and behaviour

Theme: Neuroendocrine and autonomic nervous systems

36.01. The influence of prenatal stress, anxiety and depression on fetal and child neurodevelopment, and underlying biological mechanisms

Professor Vivette Glover - *Imperial College London, UK*

Prenatal stress, anxiety and depression increase the risk for a range of neurodevelopmental problems in the child and young adult. These include symptoms of anxiety and depression, ADHD, conduct disorder, cognitive problems, being on the autistic spectrum and schizophrenia. Population studies have controlled for a range of possible other influences, including postnatal maternal mood, showing the causal role of the prenatal period. Most children are not affected, and those that are can be affected in different ways, depending in part on the genetic vulnerabilities of each child. The biological mechanisms underlying this fetal programming are starting to be understood, with studies focussing on the HPA axis, although many other systems are likely to be involved also.

The relevant changes in biology of the mother are still not clear. The maternal HPA axis becomes less sensitive to stress as pregnancy progresses. Pro-inflammatory cytokines may play an important role. The function of the placenta has been found to be altered in association with prenatal anxiety and depression, with a decrease in expression and activity of the enzyme 11b-HSD2, which metabolises cortisol, and an increase in the expression of the glucocorticoid receptor, thus potentially exposing the fetus to higher levels of cortisol. Raised amniotic fluid cortisol levels have been found to be associated with a lower cognitive ability of the infant and with altered functional MRI scans of the child. These placental changes have been found in Caucasians, but not in some non-Caucasians, suggesting the possibility of ethnic differences in these effects.

These effects of prenatal maternal mood on child neurodevelopment suggest that better prenatal emotional care of pregnant women may help to improve child outcome.

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36.02. Can the adverse effects of prenatal stress on the offspring's brain and behaviour be prevented by targeting the placenta?

Dr Paula Brunton - *University of Edinburgh, UK*

Exposure to early life stress can programme persistent neural and behavioural changes. Often this programming is maladaptive, increasing the susceptibility of an individual to mood disorders (e.g. anxiety, depression), behavioural disorders (e.g. attention deficit/hyperactivity disorder) and cognitive impairments. Using a rat model, we have demonstrated that exposure to social stress during pregnancy results in greater hypothalamo-pituitary-adrenal (HPA) axis responses to stress, heightened anxiety behaviour and social memory impairments in the adult offspring. The mechanisms involved in transmitting the effects of maternal stress to the foetuses are unclear, however as the maternal-fetal interface, the placenta is likely to play a key role. Indeed, in response to hypoxia, placental secretions increase the production of reactive oxygen species and damage developing neurones. Moreover, evidence suggests psychosocial stress increases oxidative stress in rats. The antioxidant, mitoquinone, attached to a nanoparticle delivery system (MitoQ-NP) prevents placental secretion of these factors in vitro. Hence, the aim here was to investigate whether maternally administered MitoQ-NP can prevent the adverse effects of prenatal stress (PNS) exposure in the offspring.

Pregnant rats were administered either MitoQ-NP or vehicle on day 16 of gestation and were then left undisturbed or subjected to social stress for 5 days. Heightened anxiety-like behaviour in PNS offspring was prevented by maternal MitoQ-NP treatment. PNS offspring did not exhibit a depressive-like phenotype in the forced swim test compared with controls, however MitoQ-NP had an antidepressant-like effect regardless of prenatal treatment. Maternal mitoQ-NP did not alter the corticosterone secretory response to acute stress in either control or PNS offspring; nor did it prevent social memory deficits in the PNS offspring.

In conclusion, maternal anti-oxidant treatment prevents anxiety-like behaviour, but not HPA axis dysregulation or social memory deficits induced by prenatal stress. Moreover, maternal MitoQ-NP treatment evidently has anti-depressive effects in the offspring.

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36.03. Transgenerational accumulation of impairments in maternal behaviour following postnatal social stress

Dr Chris Murgatroyd - *Manchester Metropolitan University, UK*

Early environment such as maternal care can have long-term physiological and behavioral effects on offspring and future generations. Exposure to chronic social stress (CSS), an ethologically model of postpartum depression and anxiety, during lactation impairs maternal care and exerts similar effects on the F1 dam offspring of the stressed F0 dams. These changes associate with increased corticosterone and neuroendocrine alterations. CSS F2 offspring further display decreased social behavior as juveniles and adults and decreased basal levels of corticosterone.

We investigated the transgenerational inheritance of alterations in maternal behavior in F2 CSS dams together with neuroendocrine and immune markers to explore whether aspects of maternal behavior are transgenerationally inherited through immune and neuroendocrine mechanisms.

We found that maternal care behavior in the F2 dams is more severely impaired than in the F0 and F1 dams and the expression of maternal anxiety is expanded in F2 dams. This occurred together with reduced basal cortisol (in contrast to an increase in F1 dams), a lack of changes in neuroendocrine gene expression, and reduced serum ICAM-1 (intercellular adhesion molecule-1) levels - a marker for inflammation and blood-brain barrier integrity.

The results support the hypothesis that the effects of chronic social stress can accumulate across three generations to depress maternal care, increase maternal anxiety, and alter basal functioning of the immune system and hypothalamic pituitary adrenal axis.

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36.04. Programming effects of peripubertal stress on brain and behaviour

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Early life stress is recognized as an important contributing factor in the programming of future behavioral outcomes. Adolescence is a particularly critical developmental window when stress can exert extensive influence on brain and behavior. In this talk, I will focus on the long-term consequences of peripubertal stress on rats' socio-affective and cognitive behavior. I will also address neurobiological mechanisms in the amygdala and prefrontal cortex (PFC) that could underlie these behavioral effects. Peripubertally stressed animals show decreased interest in social interaction and increased aggression during adulthood. These behavioral changes were observed in the context of reduced protein and mRNA levels of GABAergic markers in the amygdala, whereas there were indications for increased glutamatergic markers. Regarding cognitive behavior, adult rats that have been exposed to peripubertal stress show impaired attention in the five-choice serial reaction time task. Reduced mRNA levels of neuroligin-2 (NLGN-2), a synaptic cell adhesion molecule located at inhibitory synapses, were found in the PFC of adult rats that had been subjected to stress as adolescents. Notably, adeno-associated virus-induced rescue of NLGN-2 in the PFC reversed the stress-induced attention deficits, establishing a strong link between cognitive performance deficits following peripubertal stress and NLGN-2 availability. These findings are providing insight into the neurobiological mechanisms of the effects of stress during adolescence and can thus prove useful in the design of treatment strategies in a preclinical context.

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