BNA2017 TALK ABSTRACTS
SESSION 2TUESDAY 11TH APRIL

Symposium 10 – Microglia, neuroinflammation and psychiatric disease: biomarkers and therapeutic potential

Theme: Neuronal, glial and cellular mechanisms

10.01. The functions of microglia and their diverse activation states

Professor Hugh Perry - *University of Southampton, UK*

The microglia are the resident macrophages of the brain, they are derived from the yolk sac and populate the embryonic brain. They are maintained by local division with little replacement or recruitment from circulating monocytes. Microglia in the adult brain adopt a distinct morphology and phenotype that sets them apart from other tissue macrophages. A growing number of functions in the developing and adult brain have been attributed to microglia including the removal of apoptotic cells, surveillance and removal of supernumerary synapses – so called synaptic stripping- and many others. Apart from these homeostatic functions microglia rapidly respond to perturbations of their local environment and become activated. These activated microglia alter their morphology and phenotype and have often been described in terms of an M1 or M2 phenotype, which is unlikely to reflect the phenotype or potential of these cells in vivo. The microglia are highly plastic cells, and exist in diverse states with the potential to rapidly change in response to other stimuli arising both from within and outside the brain. The relevance of these findings for psychiatric disease will be discussed.

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10.02. Therapeutic modulation of microglia – opportunities and challenges

Dr Irene Knuesel - *Roche, Switzerland*

As the resident immune cells of the central nervous system, microglia play key roles in CNS maintenance, including refinement of synaptic networks, phagocytosis of cellular debris, and secretion of neurotrophic factors. They actively survey the environment for the presence of pathological elements such as neuronal death or protein aggregates (1). On the other hand, their activation is not only essential to brain recovery and repair; sustained activation or deregulated responses may exacerbate brain injury and play a major role in neuronal cell damage and death by releasing a variety of inflammatory and neurotoxic mediators (2-4). In addition, aged microglia undergo striking molecular changes which affect their neuroprotective functions, ultimately leading to a failure in proper damage response during aging and resulting in progressive neurodegeneration (5). The full range of microglial activities is still not completely understood, but there is strong genetic evidence supporting a crucial role for both innate and adaptive immunity dysfunction in aging-associated neurodegenerative disorders (6). The seminar will cover recent progress in our understanding of both deleterious and beneficial effects of microglia in the setting of chronic neurological insults, and the emerging concepts surrounding pharmacological therapeutic interventions.

Cited References:

1) Knuesel et al. Nat Rev Neurol. 2014; 10:643-60.

2) Ramanan et al. Brain. 2015; 138:3076-88.

3) Kreisl et al. Brain. 2013; 136:2228-38.

4) Hamelin et al. Brain. 2016; 139:1252-64.

5) Streit and Xue. Curr Opin Immunol. 2014; 29:93-6.

6) Gagliano et al. 2016, in press.

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10.03. Biomarkers of inflammation and treatment response in psychosis and depression

Professor Carmine Pariante - *King's College London, UK*

The presence of increased inflammation in patients with mental disorders is one of the most important recent developments in mental health and clinical neuroscience. Most of the data derive from studies in depression, where there is consistent evidence that around one-third of patients presents with high levels of inflammation. We have shown that these patients are more likely to have a more enduring form of depression, with a genetic component or a neurodevelopment trajectory that starts with exposure to stress early in childhood or even in utero. Most importantly, we have also shown that these patients are less likely to respond to conventional antidepressants, and current clinical trials are testing whether they are more likely to respond to combinations of antidepressants with anti-inflammatories. In schizophrenia and psychotic disorders there is less research, but some evidence that increased inflammation is present in a subgroup of patients that do not respond to conventional antipsychotics is also emerging. Together, these studies demonstrate a new important role of increased inflammation in the pathogenesis and treatment of mental disorders.

Funding: Funded by the Medical Research Council, the Wellcome Trust and NIHR BRC at Maudsley and King's College London, as well as from research grants from Johnson & Johnson and two MRC/Wellcome-led Consortiums that also include GSK, Johnson & Johnson, Pfizer and Lundbeck. In the last 12 months, Professor Pariante has received speakers fee from Lundbeck and consultancy fees from Eleusis Benefit Corporation.

References:

Baumeister D, et al. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-?. Mol Psychiatry. 2016 May;21(5):642-9.

Cattaneo A, et al. Absolute Measurements of Macrophage Migration Inhibitory Factor and Interleukin-1-? mRNA Levels Accurately Predict Treatment Response in Depressed Patients. Int J Neuropsychopharmacol. 2016 Sep 30;19(10).

Barnes J, et al. Genetic Contributions of Inflammation to Depression.

Neuropsychopharmacology. 2017 Jan;42(1):81-98.

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10.04. Genome-wide transcriptional profiling and structural magnetic resonance imaging in the maternal immune activation model of neurodevelopmental disorders

Dr Anthony Vernon - *King's College London, UK*

Prenatal exposure to maternal infection increases the risk of schizophrenia and autism1, but the molecular processes underlying this association are only partially understood. Through a collaborative network, we sought to address this by exploring convergent molecular and neuroanatomical alterations in corticostriatal areas of a well-characterized developmental immune activation model with relevance to schizophrenia2.

Developmental immune activation was induced by treating pregnant C57BL6 mice with the viral mimic poly(I:C) on gestation day 173. The offspring of immune-challenged and control mothers were first assigned to behavioural testing in pubescence and adulthood, followed by unbiased genome-wide transcriptional profiling with follow-up epigenetic analyses3. Separate cohorts of offspring also underwent ex vivo structural magnetic resonance imaging3.

Immune challenged offspring displayed behavioural impairments relevant to schizophrenia, including deficits in prepulse inhibition and working memory3.

Genome-wide transcriptional profiling revealed that prenatal immune activation caused a differential expression of 116 and 251 genes in the medial prefrontal cortex and nucleus accumbens, respectively. Genes that were commonly affected in both brain areas were related to myelin functionality and stability3. Epigenetic analyses indicated that altered DNA methylation of promoter regions might contribute to the differential expression of these myelin-related genes3. MR imaging revealed increases in T1 relaxation times and consistent reductions in T2 relaxation times, but sparse anatomical changes3.

This powerful multi-systems approach demonstrates that prenatal viral-like immune activation causes myelin-related transcriptional and epigenetic changes in cortiostriatal areas. Whilst these abnormalities do not seem to be associated with overt white matter reduction, they may provide a molecular mechanism whereby prenatal infection can impair myelin functionality and stability.

Financial support from the Medical Research Council (MR/N025377/1) is gratefully acknowledged.

1Estes ML, McAllister AK. Science. 2016; 353(6301): 772-7.

2Meyer U. Biological Psychiatry. 2014; 75(4): 307-15.

3Richetto et al., Cerebral Cortex. 2016; DOI: 10.1093/cercor/bh

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Symposium 11 – Neuronal control of nutrition: integrating energy balance and motivation

Theme: Attention, motivation, behaviour

11.01. Neural orchestration of eating and locomotion

Dr Denis Burdakov - *The Francis Crick Institute, London, UK*

The talk will focus on deconstructing neural circuits and dynamics that co-ordinate physical activity and eating. Specific focus will be on deciphering energy-related hypothalamic signals and circuits (orexin, Agrp, GABA) in mice, using ontogenetic, chemogenetic, and in vivo cell-type-specific recording technologies.

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11.02. Sweet, light and beyond

Dr Ana Domingos - *Gulbenkian Institute of Science, Portugal*

Sugars that contain glucose, are generally preferred to artificial sweeteners owing to their post-ingestive rewarding effect, which elevates striatal dopamine (DA) release. The post-ingestive rewarding effect of sucrose, which artificial sweeteners do not have, occurs even in sweet-blind mutant mice and bias food preference. Melanin-concentrating hormone (MCH) neurons are located in the lateral hypothalamus projecting to reward-related areas, and are glucose sensitive. We showed that optogenetic activation of MCH neurons during intake of the artificial sweetener sucralose increases striatal dopamine levels and inverts the normal preference for sucrose vs sucralose. We also show that loss of MCH neurons suppresses sucrose to sucralose preference and lead to reduced striatal DA release upon sucrose ingestion. MCH neurons are required for the post-ingestive rewarding effect of sucrose in sweet-blind mutant mice. These studies delineate an essential component of the neural circuit linking nutrient sensing and sugar reward. More recently we have used optogenetics to discover that peripheral neurons directly controlling fat mass depletion. Leptin is a hormone produced by the adipose tissue that acts in the brain, stimulating white fat breakdown. We find that the lipolytic effect of leptin is mediated through the action of sympathetic nerve fibers that innervate the adipose tissue. Using intravital two-photon microscopy, we observe that sympathetic nerve fibers establish neuro-adipose junctions, directly “enveloping” adipocytes. Local optogenetic stimulation of sympathetic inputs induces a local lipolytic response and depletion of white adipose mass. Conversely, genetic ablation of sympathetic inputs onto fat pads blocks leptin-stimulated phosphorylation of hormone-sensitive lipase and consequent lipolysis, as do knockouts of dopamine β-hydroxylase, an enzyme required for catecholamine synthesis. Thus, neuro-adipose junctions are necessary and sufficient for the induction of lipolysis in white adipose tissue and are an efferent effector of leptin action. Direct activation of sympathetic inputs to adipose tissues may represent an alternative approach to induce fat loss, circumventing central leptin resistance.

http://www.cell.com/cell/abstract/S0092-8674(15)01107-1

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11.03. Why did I eat that? Differences in striatal function and motivation that contribute to obesity

Dr Carrie Ferrario - *University of Michigan, USA*

While urges to eat are regulated by hunger, satiety, and energy demand, they are also strongly influenced by stimuli in the environment that are associated with food (food cues). For example, in non-obese people, food cues increase food craving and consumption. Obese people are more sensitive to these motivational properties of food cues, reporting stronger cue-triggered food craving and consuming larger portions after food cue exposure. Additional human studies suggest that cue-triggered craving in obese individuals involves alterations in function of the nucleus accumbens (NAc), a region that mediates motivation for food and drug rewards, and that is increasingly implicated in obesity. For example, human fMRI studies show that activations in the NAc triggered by food cues are stronger in obese people. In addition, enhanced responsivity in the NAc to food cues predicts future weight gain and difficultly losing weight in humans. These data suggest that interactions between susceptibility and consumption of sugary, fatty foods may enhance NAc activity to enhance motivation and facilitate weight gain [1]. AMPA receptors (AMPARs) excitatory drive to the NAc, and cue-triggered food-seeking relies in part on activation of NAc AMPARs. Thus, we began a series of studies to examine how alterations in NAc AMPAR transmission contribute to cue-triggered food-seeking in obesity susceptible and resistant rat models. Using whole-cell patch clamping and biochemical approaches, we have found that consumption of sugary, fatty “junk-foods” increases NAc AMPAR-mediated expression and transmission in obesity-prone, but not obesity-resistant rats [2], even prior to the development of obesity. The unpublished data presented in this talk will expand upon this initial study by showing that increases in NAc AMPAR-mediated transmission mediate enhanced cue-triggered food-seeking in obesity-prone vs. obesity resistant rats. Implications for the development and persistence of obesity will be discussed [3].

Funding: NIH NIDDK: R01DK106188; 3R01DK106188-02-S1; 31DK111194; FDK112627A; NIDA: NIDA T32DA007268.

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2.Oginsky, MF, et al; Neuropsychopharmacology, 2016. 41(13): p.2977-2986

3.Ferrario, CR; Neuropsychopharmacology, 2017. 42(1): p.361

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11.04. Mesolimbic response to energy and other nutrients

Dr James McCutcheon - *University of Leicester, UK*

Efficient foraging behaviour relies on linking the taste and nutritional value of food with environmental stimuli that predict the food’s availability. Mesolimbic circuitry, including dopamine projections from the midbrain, is an important substrate of these processes. As well as procuring enough energy to survive, it is also important to acquire sufficient macro- and micro-nutrients to fulfil metabolic demands. As such, the value of a food is based not only on its energetic content but will also be sensitive to an interaction between the food’s nutritional profile and an animal’s physiological state. For example, if animals are depleted of a specific nutrient then foods that counteract this depletion may be favoured. We have used multiple in vivo techniques to understand how nutritional value is encoded in the brain with a focus on mesolimbic circuitry. Previously, we used fast-scan cyclic voltammetry to show that phasic dopamine is modulated by the energetic value of food with sucrose evoking a greater dopamine response than saccharin (McCutcheon et al 2012). Currently, we are using intragastric infusions in combination with fibre photometry to understand how neural populations downstream of this dopamine signal in the nucleus accumbens are affected by energetic value. In addition, we are exploring appetite for specific nutrients, in particular dietary protein. When rats are maintained on a low protein diet, they develop an appetite for protein and we observe altered activity in mesolimbic circuits. Thus, similar to our previous work with sodium (Cone et al 2016), physiological state seems to gate both behaviour towards specific nutrients and associated neural responses. Thus, in summary, nutritional value, conceptualised as energetic content or nutrient profile, is relayed to and encoded by mesolimbic circuitry. It is therefore likely to be a crucial determinant in generating appetite and food-seeking behaviour and future work aims to tease out these mechanisms.

Funding: BBSRC, EC, and NIH.

Cone et al (2016) Physiological state gates acquisition and expression of mesolimbic reward prediction signals. PNAS 113:1943-8

McCutcheon et al (2012) Sucrose-predictive cues evoke greater phasic dopamine release than saccharin-predictive cues. Synapse 66:346-51

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Symposium 12 – Old brains, new insights

Theme: Neurodegenerative disorders and ageing

12.01. Nimble forgetfulness in healthy ageing

Professor Anna Christina Nobre - *University of Oxford, UK*

Our advancing years bring along frustrating deficits in long-term and short-term memory. Attention functions have been strongly linked to memory functions, with the two proposed to coexist in a mutually supportive relationship. The ability to focus on relevant items improves the likelihood of successful retrieval; in turn, short-term and long-term memory representations guide attention to improve selection of relevant item. Recently, deficits in using proactive and selective attention have been suggested as a hallmark of ageing, which has cascading effects on the quality of memory. We have addressed this possibility by testing healthy older participants in tasks specifically looking at the interaction between selective attention and memory – both short-term memory and long-term memory. Our findings consistently show preservation of flexible attention-related mechanisms in the context of memory-related deficits. Recordings of brain activity using magnetoencephalography in a large group of older individuals show that individual differences in short-term memory performance correlate with neural markers of efficient top-down attention control. So far the findings suggest that, rather than adding to cognitive deficits in healthy ageing, selective attention can be preserved and may acts as a means to bolster cognition.

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12.02. Finding the ageing brain's natural capacity

Dr Karen Campbell - *Brock University, Canada*

Our understanding of how age affects the mind and brain is largely based either on tightly controlled, though largely artificial, experimental tasks or, on the completely uncontrolled resting state. Neither of these approaches is ideal, as the former introduces a number of task demands (e.g. decision making, responding) that are usually external to the cognitive process under investigation (e.g., language comprehension), while the latter offers no control over participants' thoughts whatsoever. In this talk, we advocate for a naturalistic approach to neurocognitive ageing, by driving neural activation with stimuli that more closely approximate everyday life and measuring age differences (or lack thereof) in resulting network responsivity/connectivity.

Data are taken from the Cambridge Centre for Ageing and Neuroscience (Cam-CAN) cohort, a large population-derived sample of 700 people aged 18-88 years with a rich combination of cognitive, lifestyle, and neuroimaging data.

a) We show that during naturalistic viewing (i.e., movie-watching) neural synchrony declines with age, such that older adults respond to life-like scenarios in a much more idiosyncratic way. Decreased neural synchrony related to measures of attentional control, suggesting that it results from differential patterns of attention. Thus, age differences in attention are not limited to cognitive tasks, but likely affect our processing of events in everyday life, resulting in a more individualised experience of the world as we age.

b) In a second study, we show that age differences in attentional control may also underlie excess frontal activations commonly attributed to "compensation". Using independent components analysis and a language comprehension paradigm, we show that while natural task-free language comprehension only activates the auditory and frontotemporal language networks, performing a simple task with the same sentences activates several additional networks, and it is these task-related networks that differ with age while sentence comprehension remains unchanged.

Taken together, these studies show that age differences in attention are pervasive and can interact with artificial task demands to affect our understanding of those processes which are otherwise preserved with age.

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12.03. Multi-scale integrative network dynamics (MIND) of the ageing brain: a new model of neurocognitive ageing and function

Dr Kamen Tsvetanov - *University of Cambridge, UK*

The preservation of cognitive function is critical for well-being across the lifespan and requires homeostatic and resilient systems of brain function. Previous studies of ageing provide a partial understanding of these systems, usually described in terms of neural signals from local brain activity or covariance among activations (network connectivity) and higher order interactions between such brain networks (e.g, “default mode network” interaction with the “salience network”).
We propose that the effects of ageing on brain function can best be identified in a set of high-dimensional spatio-temporal “fingerprints”, which can be characterized from brain imaging using activity and connectivity metrics derived from functional magnetic resonance connectivity (fMRI) and magnetoencephalography (MEG). The combination of spatio-temporal representations of neural activity and connectivity on multiple spatial and temporal scales provides a new approach which we call “multi-scale Integrative network dynamics” (MIND).
I will introduce MIND, building on methods that demonstrate the ability to represent more accurately neural signals (e.g. by separating neural from vascular contributions to fMRI BOLD signal) in a large population-based cohort (www.cam-can.com). I will show the behavioural relevance of joint connectivity and activity signals, to cognitive function with age, and then present initial studies in support of MIND in the context of cognitive control systems. The joint consideration of activity and connectivity within distributed networks provides a rich description of the repertoire of brain dynamics across the lifespan with implications for our understanding the normal process of individual differences, ageing and neurodegenerative disorders.

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12.04. Constrained moment-to-moment brain signal variability as a principled marker of the ageing brain

Dr Douglas Garrett - *UCL and Max Planck Institute, Germany*

Neuroscientists have long observed that brain activity is naturally variable from moment-to-moment, yet neuroimaging research rarely considers signal variability as a within-person measure of interest. Our work on younger and older adults suggests that within-person brain signal variability offers highly predictive, complementary, and even orthogonal views of brain function compared to traditional measures. In particular, we continue to find that older, poorer performing adult brains often exhibit less signal variability, within and across brain regions and tasks. Accordingly, I will discuss the idea that contrary to traditional theoretical expectations of adult-developmental increases in "neural noise," brain aging could instead be re-conceived of as a generalized process of increasing system rigidity and loss.

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Symposium 13 – Young people’s mental health: uniting the sciences to find answers

Theme: Psychiatry and mental health

13.01. Early adversity and psychotic experiences: bio-psycho-social pathways and resiliencies

Dr Helen Fisher - *King’s College London, UK*

Psychotic experiences are reported by approximately 1 in 10 children at 12 years of age and include paranoid thoughts, hearing or seeing things that others do not, and believing that others can read one’s mind. These experiences are often distressing and highly predictive of schizophrenia, other psychiatric disorders and suicide in adulthood, particularly if they persist during adolescence. Moreover, these sub-clinical phenomena are a major risk factor for self-harm and suicide attempts in adolescence. Therefore, the aetiology of these early psychotic experiences and the mechanisms underlying their persistence urgently require further investigation to facilitate early identification of children at increased risk in order to optimally target preventive interventions. To begin to address these important questions, data were utilised from the Environmental Risk (E-Risk) Longitudinal Twin Study, an epidemiological study of 2,232 children (1,116 twin pairs) and the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort of 14775 children born in Bristol, both followed to age 18. Comprehensive assessments (including collection of biological samples) were repeatedly conducted with mothers and children throughout childhood and adolescence. This talk will present findings demonstrating that biological (DNA methylation patterns) and psychosocial (exposure to multiple forms of victimisation and threatening neighbourhoods) factors are associated with the onset and persistence of psychotic experiences in these children. Moreover, it will be demonstrated that children’s characteristics, family context, and the wider community they are brought up in can protect children from developing psychotic experiences, even when they have been victimized multiple times. The future integration of these findings and their implications will be discussed.

Funding:

This project was funded through an MQ Fellows Award to Dr Fisher (MQ14F40). The E-Risk Study is funded by the MRC (G1002190), NICHD (HD077482), Jacobs Foundation, MRC and ESRC PhD studentships, and the British Academy (SQ140024). ALSPAC is funded by the MRC and the Wellcome Trust (102215/2/13/1) and the University of Bristol. ARIES was funded by the BBSRC (BBI025751/1 and BB/I025263/1).

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13.02. Environmental risks and social behaviour - translational approaches

Dr Nichola Brydges - *Cardiff University, UK*

Adverse experiences early in life significantly increase the risk of developing neuropsychiatric disorders later in life. Abnormalities in social functioning are a key component of many of these disorders, however, the underlying mechanisms linking early life adversity with altered social function are not well understood. Our research uses translational approaches to investigate the relationship between early life adversity and social behaviour in adulthood.

Using an animal model, we assessed the impact of exposure to short term stressors during the pre-pubertal phase on social behaviour later in life. Rats experienced stress during postnatal days 25-27. In adulthood, these animals were introduced to unfamiliar rats from the same treatment group, and their interactions were recorded and scored. Animals exposed to stress were faster to initiate contact and demonstrated reduced contact duration. They also vocalised significantly less than control animals during social interactions. Arginine vasopressin (AVP) levels were significantly elevated in the plasma of stressed animals, whereas oxytocin levels were unchanged. Hypothalamic mRNA levels of oxytocin, AVP and their receptors (OXTR and AVPR1a) were similar between groups. AVP and oxytocin play central roles in stress responses and social interactions. Therefore, increases in AVP following pre-pubertal stress may underlie alterations in social interactions. Further work is needed to clarify this.

Deficits in social functioning are also correlated with exposure to childhood trauma in humans. We found that individuals with borderline personality disorder (BPD), a condition associated with childhood trauma, exhibited impairments in correct identification of emotional facial expressions and measures of social judgement, and these deficits correlated with a measure of childhood trauma1,2. We are currently extending this work by assessing AVP levels in this patient group to investigate its potential relationship to childhood trauma and social behaviour in BPD.

1. Nicol, K. et al. 2013. PLOS One 8, e73440

2. Nicol, K. et al. 2014. Psychiatry Research 218, 256-258.

Funding: The Waterloo Foundation, NMHRI Fellowship.

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13.03. The hidden wounds of childhood trauma: psychoneuroimmunology of early stress and the impact on mental health

Dr Andrea Danese - *King's College London,UK*

Childhood maltreatment is arguably the most common, modifiable risk factor for psychopathology. Yet, the mechanisms through which childhood maltreatment affects psychopathology remain unclear. We tested the effects of maltreatment on inflammation, a key pathway in the pathophysiology of several psychopathological conditions.

We tested this association in members of the New Zealand Dunedin Multidisciplinary Health and Development Study, which involves 1,000 children born in 1972–73. Childhood maltreatment was prospectively assessed during the first decade of life and inflammation levels were measured at age 32 years.

We found that maltreated children had high levels of multiple blood biomarkers of inflammation in adulthood compared to non-maltreated children [1]. These abnormalities were not explained by the influence of co-occurring early-life risks, stress in adulthood,

and adult health and health behaviours. Inflammation levels were particularly elevated in maltreated children who had depression at the time of assessment in adult life. These findings were replicated in the U.K. Environmental Risk (E-Risk) Longitudinal Twin Study, which involves 2,000 children born in 1972–73. The findings have been replicated in more than two dozens other studies and back-translated to animal models.

We suggest that inflammation could contribute to risk for psychopathology in maltreated individual. These findings have important implications for future research and treatment [3].

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[1] Danese, A., Pariante, C.M., Caspi, A., Taylor, A., Poulton, R. Childhood maltreatment predicts adult inflammation in a life-course study. Proc Natl Acad Sci U S A. 2007; 104(4):1319–24. doi: 10.1073/pnas.0610362104

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FUNDING

U.K. MRC, U.S. NIH, NARSAD, ESRC

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13.04. Genetic and environmental impact in psychosis

Dr Jim van Os - *Maastricht University, The Netherlands*

Bringing together genetic and environmental influences impacting on the liability to suffer psychotic disorder represents a major challenge. We used summary molecular measures of genetic risk (polygenic scores -G) and measures of early environmental adversity, cannabis use and urban environment (E) to examine G and E effects on psychosis-related phenotypes of depression, aberrant salience and neurocognitive impairment in a large national sample of patients, relatives and controls. Both G and E impact on psychosis-related phenotypes - but in different fashions across different phenotypes and with little evidence of synergistic interaction.

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Symposium 14 – Neural mechanisms underlying autonomic responses to stress

Theme: The neurobiology of stress

14.01. Control of cardiovascular responses to acute emotional stress by corticotropin-releasing factor in the bed nucleus of the stria terminalis: Involvement of local NMDA-NO-GMPc-PKG signaling mechanism

Dr Carlos Crestani - *Universidade Estadual Paulista (UNESP), Brazil*

Activation of corticotropin-releasing factor (CRF) receptors within the bed nucleus of the stria terminalis (BNST) facilitates the local release of glutamate. NMDA-glutamate receptor activation results in nitric oxide (NO) formation that in turn activate cyclic guanosine monophosphate (cGMP)-cGMP-dependent protein kinase (PKG) signaling pathway. Despite these pieces of evidence, a possible interaction between these neurochemical mechanisms in control of cardiovascular responses to stress has never been investigated. Thus, here we evaluated an involvement of local NMDA-NO-cGMP-PKG signaling mechanism in control of the cardiovascular responses to acute restraint stress by CRF within the BNST in rats. For this, male Wistar rats had cannula-guides bilaterally implanted into the BNST. A catheter was implanted into the femoral artery for mean arterial pressure (MAP) and heart rate (HR) recording. Tail skin temperature was recorded using a thermographic camera. Animals received bilateral microinjection into the BNST of the NMDA receptor antagonist LY235959 (0.5nmol/100nL), the selective neuronal NO synthase enzyme (nNOS)

inhibitor N?-Propyl-L-arginine (NPLA) (0.2nmol/100nL), the soluble guanylate cyclase inhibitor ODQ (0.5nmol/100nL), the cGMP-dependent protein kinase (PKG) blocker KT5823 (0.1nmol/100nL), or saline (100nL). Five minutes later, CRF (0.07nmol/100nL) or saline (100nL) was microinjected into the BNST. Five minutes after BNST pharmacological treatment rats underwent a 30 min session of restraint. Bilateral microinjection of CRF into the BNST enhanced the MAP ($P<0.0001$) and HR ($P<0.0001$) increase caused by restraint stress, without affecting the drop in skin temperature ($P>0.05$). Pretreatment of the BNST with either LY235959, NPLA, ODQ, or KT5823 completely abolished the effects of CRF on restraint-evoked pressor ($P>0.05$) and tachycardiac ($P>0.05$) responses. These results provide evidence that the facilitatory influence of CRF neurotransmission into the BNST in cardiovascular responses to stress is mediated by activation of local NMDA-NO-cGMP-PKG signaling mechanism.

Financial support: The Physiological Society, FAPESP, CNPq, and PADC/FCF-UNESP.

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14.02. Microglia soothe the sympathoexcitatory response to seizure

Dr Paul Pilowsky - *University of Sydney, Australia*

Epileptic seizures exhibit specific clinical syndromes that include changes in motor function, and loss of consciousness. The causes of epilepsy are not always easy to determine, but whatever the cause a frequent complication of epilepsy is dysautonomia, although this is not well characterised. Dysautonomia manifests as a complex of symptoms including hypertension, arrhythmia, and hyperthermia and is most likely due to an overactivity of sympathetic neurons. However, neurons are not the only cell type present in the sympathetic nervous system. Microglia, the brain's immune cells, are of particular importance. Work from our laboratory has revealed that microglia restrain the seizure-induced sympathoexcitation (1, 2). In the spinal cord, antagonism of PACAP receptors, or microglia, both enhance the sympathetic response to kainic acid induced seizure. In the rostral ventrolateral medulla (RVLM; a sympathoexcitatory cardiovascular nucleus), microinjection of the glutamate antagonist, kynurenic acid, abolishes the seizure induced sympathoexcitation. Antagonism of PACAP or microglia in the RVLM does not affect the sympathoexcitation, but prevents pro-arrhythmogenic changes. We conclude that the dysautonomia that occurs following seizure is related to multiple neurotransmitters acting on different cell types. Our work suggests new options for treatment of dysautonomia in epilepsy.

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2. Bhandare AM, Mohammed S, Pilowsky PM, and Farnham MM. Antagonism of PACAP or microglia function worsens the cardiovascular consequences of kainic-acid-induced seizures in rats. J Neurosci 35: 2191-2199, 2015.

Funding: National Health and Medical Research Council, HRI.

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14.03. Autonomic modifications induced by social defeat involve serotonin in the brainstem associated to activation of the dorsomedial nucleus of the hypothalamus

Dr Caroline Sévoz-Couche - *Sorbonne Universités, France*

Mood disorders are associated with the occurrence of ventricular arrhythmia. However the mechanisms involved in the dysautonomia at the origin of arrhythmia are still unknown.

The dorsal medial nucleus of the hypothalamus (DMH) contributes to acute arousal responses in stress situation, and its stimulation causes sympathetic activation coupled to baroreflex parasympathetic inhibition through secondary activation of 5-HT3 receptors in the nucleus tractus solitarius (NTS). We therefore evaluated the possible involvement of the DMH and NTS 5-HT3 receptors in the dysautonomia induced by anxiety.

We used an original model of chronic stress based on anticipatory social defeat, that induced an anxiety- like state in defeated rats. Using our paradigm, we were able to modelize long-term stress-evoked cardiac baroreflex reduction. The central pathway involved in these modifications involves DMH activation. Downstream to the DMH, a decrease in baroreflex gain and parasympathetic

activity via NTS 5-HT3 receptor excitation, and an increase in sympathetic tone independently of the NTS, are triggered. Continuous ECG recordings by telemetry demonstrated that arrhythmias occur in parallel to baroreflex inhibition, suggesting a pivotal role of NTS 5-HT3 receptors in this harmful effect induced by anxiety.

Our data bring the possibility that systemic treatment with a specific 5-HT3 receptor antagonist like granisetron —a potent anti-emetic with a highly safe profile— could be used to improve parasympathetic activity and, thus, to reduce the likelihood of adverse cardiac events in patients with high anxiety scores and in patients with induced dysautonomia, as observed after ischemic stroke, for example.

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14.04. Cardiac autonomic and respiratory correlates of high-anxiety behaviour in rats: potential involvement of the endocannabinoid signaling

Dr Luca Carnevali - *University of Parma, Italy*

Numerous studies suggest that high trait-anxious individuals are at greater risk for developing respiratory and cardiovascular disorders. Research with valid and reliable animal models can (i) offer important insights into the neurobiological bases of the comorbidity between anxiety and respiratory and cardiovascular disturbances, and (ii) guide the development of new anti-anxiety therapies which may also be useful for preventing and/or treating respiratory and cardiovascular symptoms. By using the high/low anxiety-related behavior (HAB/LAB) rodent model, in our studies we first aimed at characterizing respiratory (via plethysmographic recordings) and cardiac autonomic (via heart rate variability (HRV) analysis of ECG recordings) correlates of high-anxiety behaviour in rats. We found that adult male HAB rats exhibit (i) a higher resting respiratory rate, (ii) reduced sniffing in novel environment, (iii) increased incidence of sighs, and (iv) no habituation of the respiratory response to repetitive stressful stimuli compared to LAB animals. Moreover, HAB rats show signs of (i) impaired autonomic modulation of heart rate (low vagally-mediated HRV), (ii) poor adaptive heart rate responsiveness to stressful stimuli, (iii) increased vulnerability to isoproterenol-induced ventricular arrhythmias, and (iv) cardiac hypertrophy. Prompted by these findings, we then tested the hypothesis that pharmacological augmentation of endocannabinoid signaling, which has been recently implicated in the regulation of emotional states and cardiovascular function, would exert anxiolytic-like and cardioprotective effects. In HAB rats, acute pharmacological inhibition of the endocannabinoid anandamide-degrading enzyme, fatty acid amide hydrolase (FAAH), with URB694 (0.3 mg/kg), (i) decreased anxiety-like behavior, (ii) reduced isoproterenol-induced occurrence of ventricular arrhythmias, and (iii) corrected pro-arrhythmic alterations of ventricular refractoriness. Taken together, these findings highlight the utility of the HAB/LAB model for investigating the mechanistic bases of the link between anxiety and respiratory and cardiovascular disorders, and suggest that inhibition of FAAH might be a viable pharmacological strategy for the treatment of anxiety-related cardiac dysfunction.

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Symposium 15 – Synaptic plasticity in physiological contexts

Theme: Neuronal, glial and cellular mechanisms

15.01. TNF-α dependent spine scaling after deprivation is localized in dendritic branches that have undergone recent spine loss

Dr Tara Keck - *UCL, UK*

Homeostatic synaptic scaling is thought to occur cell-wide. We used repeated in vivo two-photon imaging in mouse visual cortex after sensory deprivation to measure TNF-? dependent increases in spine size as a proxy for synaptic scaling in vivo in both excitatory and inhibitory neurons to investigate the spatial extent of spine scaling. We found that after sensory deprivation, increases in spine size are restricted to a subset of dendritic branches, which we confirmed using immunohistochemistry. We found that the branches that had individual spines that increased in size following deprivation, also underwent a decrease in spine density. Within a given dendritic branch, the degree of spine size increases is proportional to recent spine loss within that branch. Using computational simulations, we show that this compartmentalized form of synaptic scaling better retained the previously established input-output relationship in the cell, while restoring activity levels.

Funding: This work was supported by the European Research Council, the Royal Society, the Medical Research Council and the Wellcome Trust. There is no conflict of interest.

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15.02. Optogenetic STDP: shaping hippocampal networks through temporal correlations

Professor Thomas Oertner - *Hamburg University, Germany*

Long-term plasticity (LTP, LTD) not only changes the strength of synapses, but also affects the long-term structural stability of synaptic connections. Imaging individual spine synapses in hippocampal slice cultures, we find that in the days after induction of LTD, synapses with a low release probability often completely disappear. Synaptic lifetime can be rescued by LTP induction 24 h after LTD. LTP by itself stabilizes directly activated synapses, but destabilizes neighboring synapses on the same dendritic branch. To test the long-term effects of temporal correlations in pre- and postsynaptic spike trains, we used blue- and red-shifted channelrhodopsins to sequentially activate CA3 and CA1 pyramidal cells inside the incubator. Repeated sequential firing (pre-before postsynaptic neuron) led to significant and selective strengthening of the synaptic connection compared to neighboring non-transfected CA1 neurons. Even after 3 days in the incubator, Hebbian LTP was clearly detectable. Interestingly, distributing the same number of spike pairings over 1h induced much less long-term plasticity, suggesting that individual synapses perform a leaky integration of Hebbian events.

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15.03. The formation of hippocampal cognitive maps during novel environment exposure

Dr Mark Sheffield - *Northwestern University, USA*

The hippocampus is critical for the formation and storage of spatial memories. Hippocampal place-cells fire when animals move through a particular location in space and can sequentially reactivate offline, suggesting that place-cell ensembles represent a cognitive map of space and a memory of places. Two general mechanisms have been proposed to explain how cognitive maps arise in novel environments: one involves the selection of pre-strengthened cellular ensembles and the other involves de novo formation through experience-dependent synaptic plasticity. Whether one or both of these mechanisms underlie cognitive map formation remains unknown. We used high-resolution functional imaging and virtual reality to measure place-cell dynamics when mice were exposed to novel environments. We observed immediately present maps (pre-strengthened), which were then enriched during experience with delayed-onset place-fields (de novo) through dendritic spike induced synaptic potentiation during a reduced dendritic inhibition time-window. This representation was then refined such that on the following day the skeleton map receded and the delayed-onset de novo place fields made up a greater fraction of the representation than the immediate place fields. This process led to a unique representation of a novel environment, and implicates interplay between pre-strengthened cellular ensembles and experience-dependent synaptic plasticity in the formation and storage of new cognitive maps.

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15.04. Neuromodulation of dendrites and synaptic plasticity

Dr Jack Mellor - *University of Bristol, UK*

Synaptic plasticity is a fundamental process underpinning the encoding of spatial memory in the hippocampus. It is proposed that networks of synaptically coupled place cells within the hippocampus can form spatial maps of multiple environments providing a substrate for encoding spatial memory. We have shown that the activity of synaptically coupled place cells in the hippocampus can induce synaptic plasticity and that this process depends on the presence of acetylcholine suggesting a mechanism for the formation of place cell ensembles under the control of neuromodulation. Activation of muscarinic M1 receptors at postsynaptic sites relieves negative regulation of NMDA receptors by calcium activated potassium (SK) channels opening a window for the induction of synaptic plasticity. This is demonstrated by a combination of in vitro electrophysiology, 2-photon calcium imaging and 3-D biophysical modelling of spine dynamics. By measuring acetylcholine release in the hippocampus during a working memory task we found that acetylcholine is preferentially released at reward locations suggesting that the formation of ensembles of place cells by synaptic plasticity occurs preferentially at locations associated with reward. The formation of place cell ensembles is thought to be crucial for their reactivation during sharp wave ripple events which occur during rest or sleep. We show that these reactivation events can induce further synaptic plasticity providing a mechanism for the observed consolidation of memory during sleep.

This work was funded by Wellcome Trust, BBSRC, MRC, EPSRC and Eli Lilly & co.

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Symposium 16 – Neuroscience informed education

Theme: Learning and memory

16.01. Fit to study

Dr Heidi Johansen-Berg - *University of Oxford, UK*

There is growing neuroscientific evidence that physical activity has positive effects on brain and cognition. This offers a potential powerful route for impacting on educational attainment by targeting physical activity. Meanwhile, levels of physical activity among UK schoolchildren are shockingly low, with the vast majority of children failing to reach recommended activity targets.

'Fit to Study' is a research project, funded by the Education Endowment Foundation and the Wellcome Trust, which aims to investigate the effects of school-based physical activity on academic outcomes. Fit to Study is being jointly run by the University of Oxford and Oxford Brookes University. We are recruiting 100 secondary schools to participate in the trial.

This talk will discuss the aims and rationale for the Fit to Study project. We will also share insights gained through our pilot phase, which has provided useful experience of implementing large scale trials in a school setting.

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16.02. Reading, phonology and the brain

Professor Usha Goswami - *University of Cambridge, UK*

Recent neural studies of speech processing provide a novel "oscillatory" perspective on the mechanisms that the brain uses to encode speech (Luo & Poeppel, 2007). Using these insights, I will develop and explain an oscillatory "temporal sampling" neural framework for linking auditory processing to phonological development in dyslexia (Goswami, 2011). Individual differences in children's "phonological awareness" are the major factor in individual differences in reading, across languages. I will show that for English, sensitivity to rhythmic structure is core to developing good phonological skills, and that English children with dyslexia are relatively insensitive to rhythm. Rhythmic sensitivity is related to how efficiently the brain processes the energy patterns in speech. Our neuroimaging studies show that this efficiency is reduced in dyslexia. The energy patterns in speech are rhythmic, and occur at multiple temporal rates simultaneously, which correspond to the rates measured in EEG (delta, theta, beta, gamma). I will also describe multi-sensory interventions that may be able to remediate these neural/sensory rhythmic impairments for poor readers in English.

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16.03. Inhibitory control and the learning of counter-intuitive concepts

Professor Michael Thomas - *Birkbeck, University of London, UK*

In this talk, I will discuss "UnLocke", a Wellcome Trust / Education Endowment Foundation funded project evaluating the potential of training inhibitory control skills in primary age children to support their learning of mathematics and science. Children must be able to inhibit prior contradictory knowledge and misconceptions to acquire new knowledge successfully (for example, to understand that the world is round despite years of experience that it seems to be flat). This skill of "interference control" varies

between pupils, with variation evident from an early age. Disadvantaged pupils seem to have weaker control skills than their wealthier peers. Evidence from neuroscience research supports the hypothesis that inhibition control is necessary to develop the reasoning skills required in maths and science. While studies of interventions designed to improve such "executive function" skills have shown improvements on outcomes like working memory, they have often failed to show an impact on broader attainment measures. Emerging neuroscience research suggests that the inhibition needs to happen in the networks that are specific to the skills being developed, thus the need for exercises to be related to specific subject knowledge. I will discuss the work of the University of London Centre for Educational Neuroscience in developing this project.

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16.04. Engaging the brain's reward system

Dr Katie Blakemore - *University of Bristol, UK*

In a traditional classroom, students are consistently rewarded when they perform academically, typically with verbal praise or classroom points. In controlled studies of adult learning, this system of predictable, certain rewards has been shown to be less beneficial for learning and memory than providing "uncertain" rewards [1], receipt of which are at least partially determined by chance. In a recent study, the brains of adult learners who were offered the chance to receive an uncertain reward (double or nothing points with a 50/50 chance of a win or loss) experienced a deactivation of the default mode network that correlated with individual gains in learning [2], suggesting more focussed attention on the learning task and consequently improved recall of the stimulus material.

The "Sci-napse" project (funded by the Wellcome Trust and Educational Endowment Foundation) aims to test the impact of uncertain rewards in the classroom, using a games-based approach informed by our understanding of brain function. In order to test this approach to learning in the classroom, students in 70 participating schools are to be taught Year 8 science using either Test-based teaching (a standard classroom quiz with fixed point rewards), Games-based teaching (a classroom quiz with escalating points, where students may choose to game their points on a wheel-of-fortune in order to receive "double or nothing" points), or Control teaching (business as usual).

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[2] Howard-Jones, PA, Jay, TMH, Mason, A & Jones, H, 2015, 'Gamification of Learning Deactivates the Default Mode Network'. Frontiers in Psychology, vol 6.

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Symposium 17 – Genetics of language disorders: from gene mapping to biological mechanisms

Theme: Genetics and epigenetics

17.01. Genetic associations with variation in reading and language ability: present results and future directions

Professor Tim Bates - *University of Edinburgh, UK*

Reading and language were among the first traits to have formal familial, and then genetic, interpretations. This familiality and the role of genetics in it was confirmed in behaviour genetic studies. With the advent of linkage and chromosome-based techniques, molecular regions were implicated, followed by specific genes identified by fine-mapping. Reading, especially, was one of the earliest mental traits to yield reliable molecular genetic associations. In the GWAS era, reading and language have been studied with positive results. It is perhaps fair to say, however, that work in psychiatry has demonstrated that study scale must increase by orders of magnitude to take the next steps. The value of these steps will be briefly outlined. The unprecedented resolution of genomic information requires both definitions of the phenotype which articulate the genetic architecture, measurements which are efficient, low-cost, and allow combining of samples, preferably across age and nationality. Reading, spelling, and phonological buffer phenotypes will be discussed, as will results from replication of candidates, and from hypothesis-free genome-wide scans and genetic prediction scores. Neuronal migration endophenotypes implicated are linked to specific genes. Using the educational attainment GWAS and UK biobank as bases, realistic samples sizes for additional discoveries in language and reading are outlined.

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17.02. Using extreme traits to identify genetic contributions to speech and language disorders

Dr Dianne Newbury - *University of Oxford, UK*

Developmental speech and language disorders are common in childhood and presumably arise from subtle disturbances during brain development. Nonetheless, we have little understanding as to the underlying pathology of this group of disorders. They are highly heterogeneous and in the majority of cases are genetically complex. Genetic studies have identified some common variants that contribute to risk in these disorders. Nonetheless, it is accepted that larger sample sizes and more detailed genetic analyses are required to provide a framework for these variants and to generate hypotheses regarding the critical biological connections between candidate genes. It is increasingly apparent that single nucleotide polymorphisms (i.e. common variations at single bases of DNA sequence) are unlikely to fully account for the heritability of complex genetic disorders ("missing heritability"). In reality, it is likely that speech and language disorders can arise for many different reasons, each involving different combinations of underlying risk factors. In most cases, we now expect risk models to involve hundreds of genetic variants in combination with copy number variants (CNVs), gene x gene interactions, epigenetic modifications and environmental influences. Our own studies support a role for rare coding variants in speech and language disorders and suggest that these variants can be identified using relatively small, family-based sample-sets. In this talk, I will discuss how the application of new technologies may highlight conserved mechanisms of language development providing a better understanding of the biological contributions to these disorders.

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17.03. Dyslexia and cilia biology: a new link between cognition and brain asymmetries?

Dr Silvia Paracchini - *University of St Andrews, UK*

Dyslexia is a common condition affecting up to 10% school-aged children characterised by a specific impairment in learning to read. There is strong evidence that genetics plays an important role in dyslexia. Only few specific susceptibility factors have been identified so far. Unexpectedly, their functional characterization points to a role in cilia biology. Cilia are cellular organelles required in many processes including the establishment of left-right asymmetries during early development. This observation has led to revisit the investigation of the role of brain asymmetries in dyslexia (1). Atypical brain asymmetries, both structural and functional, have been consistently reported in individuals with dyslexia. Handedness has been studied in individuals with dyslexia as an accessible tool to study brain asymmetries. Recently we have identified the very first gene, PCSK6, associated at statistical level with human handedness(2). Both PCSK6 function and pathway analysis conducted in the same dataset indicate a role of the biology of structural asymmetries in contributing to dyslexia. Taken together these data suggest that the same biology underlying left/right body asymmetries might also be implicated in brain asymmetries and relevant to neurodevelopmental disorders such dyslexia (3). Current efforts are focused in both dissecting the molecular mechanism underlying genetic associations as well as at conducting larger genetic screenings to identify novel candidate genes both for handedness and dyslexia.

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3. Brandler,W.M. and Paracchini,S. (2014) The genetic relationship between handedness and neurodevelopmental disorders. Trends Mol Med, 20, 83–90.

My research is currently supported by the Royal Society and the Carnegie Trust.

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17.04. Model systems to understand language disorders: FOXP2 and beyond

Dr Sonja Vernes - *Max Planck Institute of Psycholinguistics, The Netherlands*

The capacity for speech and language is a fundamental trait of humankind, and is of intense interest across diverse fields including linguistics, anthropology, neuroscience and molecular and evolutionary biology. My research uses diverse, complementary approaches to study the genetic underpinnings of speech and language including; using clinical cohorts to investigate the genetic causes of speech and language disorders; molecular studies that demonstrate how genes influence neuronal development and function; and animal models to link gene function to behaviours relevant for spoken language. I will talk about how we use these approaches to investigate the function of genes known to be involved in speech and language phenotypes, such as FOXP2. I will also demonstrate how we have uncovered novel candidate genes by understanding the molecular functions of known disorder genes, or by interrogating often overlooked portions of the genome, such as non-coding DNA. Together, this work sheds new light on how genes and molecular networks can contribute to the aetiology of language disorders.

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Symposium 18 – The relevance of invertebrate neuroscience to food security

Theme: Sensory and motor systems

18.01. Ethologically relevant signals processed by the nematode nervous system

Dr Paul Sternberg - *California Institute of Technology, USA*

Nematodes are a highly numerous phylum and cover the gamut of ecological niches, with relevance to agriculture (plant parasites and insect biocontrol). Nematodes have about 300 neurons, the precise number depending on sex and species. We have been studying interactions of nematodes with each other, their hosts and their predators. We have identified small molecules (a family of ascarosides) that signal within species as sex attractants, aggregation pheromones and population density signals, and between species as signals for predators. We have also identified small volatile compounds made by nematodes that serve as sex pheromones; those produced by fungal predators to lure nematodes to their death; and those produced by insects that allow insect-killing bio-control nematodes to find their hosts. We study their effect primarily on Caenorhabditis elegans, seeking to understand how this worm integrates sensory inputs to alter its behavior and lifecycle. I will summarize studies from my laboratory and collaborators on how these signals are made, sensed and evolve. Some of our findings include the following. (1) We have profiled transcriptomes of some of the relevant sensory neurons, and found many 50 or more GPCRs expressed in a single neuron. The response to individual odors involves multiple receptors. (2) We find that a set of four male-specific sensory neurons act as population to sense pheromone concentration; this finding suggests that nematode neurons display very little redundancy. (3) The production of volatile pheromones by hermaphrodites or females is regulated by sperm status. (4) Our analysis of soluble and volatile sex pheromones suggest diversification and drift driven, in part, by predator-prey co-evolution.

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18.02. Socially induced phenotypic plasticity in the desert locust

Dr Swidbert Ott - *University of Leicester, UK*

Locusts are grasshoppers (Acrididae) that can transform between two extreme phenotypes known as phases [1]. This capacity has evolved in adaptation to the unpredictable precipitation patterns in their arid habitats. Locusts normally occur at very low population densities in a cryptic solitarious phase that avoids conspecifics. Sporadic rains provide opportunities for explosive population growth. The recurrence of drought then drives large numbers of locusts onto dwindling islands of verdure. This crowding triggers a rapid behavioural transition towards increased mobility and mutual attraction that is followed by slower changes in morphology and physiology. The end result is the gregarious phase, which is tailored to a life in dense mobile swarms.

Our work has focussed on the proximate causes and consequences of phase change in the Desert Locust, Schistocerca gregaria. The sole direct drivers of behavioural gregarisation are sensory stimuli from conspecifics. We have evidence that these stimuli activate specific sets of serotonergic neurones in the thoracic central nervous system. Serotonin then initiates a rapid transition to gregarious behaviour through activation of protein kinase A. The consequences of phase change extend to associative learning: the two phases use different rules to associate novel odours with toxic food. Acute crowding leaves existing food-odour associations

intact but specifically blocks the acquisition of new aversive ones. In the field, this simple mechanism enables an adaptive updating of an odour's value from aversive to appetitive.

In current work, we are exploring the relationship between behavioural plasticity and 'animal personality' in a simple paradigm that measures locomotor hesitation. This has uncovered unexpected behavioural plasticity in solitarious locusts which exceeds the phase-related reaction norm. The typical hesitant behaviour of solitarious locusts can be overridden by age or familiarity to result in a phenotype that is no less hesitant than the gregarious phase.

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Supported by research grants BB/H002537/1 and BB/L02389X/1 from the BBSRC and research project grant F/09 364/K from the Leverhulme Trust.

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18.03. Impact of neonicotinoid pesticides on bee behaviour

Professor Geraldine Wright - *Newcastle University, UK*

The impact of neonicotinoid insecticides on insect pollinators is highly controversial because these pesticides are important agricultural tools. Several studies have shown that sublethal concentrations alter the behaviour of social bees and reduce survival of entire colonies. The debate continues, however, because some studies show no effects and others use neonicotinoid concentrations that are greater than those found in the nectar and pollen of pesticide-treated plants. In the field, it is possible that bees could choose to forage on other available flowers and avoid or dilute exposure to the nectar of seed-treated or sprayed plants. Here, using a two-choice feeding assay, we show that the honeybee, Apis mellifera, and the buff-tailed bumblebee, Bombus terrestris, do not avoid nectar-relevant concentrations of the most commonly-used neonicotinoids, imidacloprid (IMD), thiamethoxam (TMX), and clothianidin (CLO). Moreover, bees of both species prefer to eat more of sucrose solutions laced with IMD or TMX than sucrose alone. By recording from the sensilla on the bees' mouthparts, we found that stimulation with IMD, TMX, and CLO neither elicited spiking responses from gustatory neurons nor inhibited the responses of sucrose-sensitive neurons. Our data indicate that bees cannot taste neonicotinoids and are not repelled by them. Instead, bees preferred solutions containing IMD or TMX even though the consumption of these pesticides caused them to eat less food overall. This implies that treating flowering crops with neonicotinoids exposes bees to substantial risk of poisoning; providing alternative plants as food sources may not reduce this threat.

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18.04. Challenges in Targeting the Neuromuscular System for Control of Agricultural Insect Pests

Dr Fergus Earley - *Syngenta, UK*

The commercially most important agricultural insecticides act at the insect neuromuscular system, through a limited number of target proteins, these being; the voltage gated sodium channel, acetylcholinesterase, nicotinic acetylcholine receptors, ligand gated chloride channels, and the ryanodine receptor. Their development has relied on the serendipitous discovery of lead molecules through their activity against the target pests, but this model of discovery is becoming less attractive, largely because of escalating costs in meeting increasingly stringent regulatory and commercial requirements. Instead the Industry is looking to exploit the knowledge that has developed around some of these target proteins in order to design novel lead molecules with improved selectivity and chemical properties. This strategy is somewhat frustrated by important gaps in our knowledge of the molecular structure and function of the most promising target proteins. For instance the molecular composition of native ligand gated ion channels in insects remains unclear and, although the existence of multiple sub-classes has been established, assignment of physiological function is lacking.

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18.05. The challenges facing the UK food system – how can neuroscience help?

Professor Guy Poppy - *University of Southampton, UK*

The global food system is becoming increasingly complex and the UK currently imports food from more than 180 countries. Food products such as Kit Kat contain multiple ingredients from countries across the world and there are more than 600 000 food businesses in the UK. The Food Standards Agency is a non-ministerial Government Department which was created after BSE and Salmonella in eggs to help restore public confidence in UK food. The principal focus of current work are modernising the regulatory system for the future and preparing for Brexit, both important to ensuring that UK consumers have food they can trust. The breadth of issues range from chemical toxicants such as BPA and acrylamide, to microbial issues such as E. coli and Campylobacter and from food allergens and intolerances through to authenticity and fraud. Ensuring that food is safe and what it says it is for all food products being consumed by UK citizens requires a lot of expertise and time resource, which is why the Internet of Things and Big Data offer unique opportunities which the FSA are exploring. The role of neuroscience in sensing for meat inspection/early warning and/or detecting animal welfare issues are just two areas in which we are currently exploring and illustrative of what might be possible.

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Symposium 19 – Neurobiological roots of brain tumours

Theme: Developmental neuroscience

19.01. Overlapping mechanisms in CNS development and gliomagnenesis

Professor David Rowitch - *University of Cambridge, UK*

Glioblastoma multiforme (GBM) is a lethal brain cancer resistant to therapy in part because of its highly invasive nature. GBMs are a highly vascular tumor with heterogeneous histological features, but they are generally considered to derive from glial lineage progenitors. We have defined Olig2, a bHLH transcription factor, as a critical determinant of oligodendrocyte progenitor identity during development. Olig2 is expressed in 100% of GBM raising the possibility of similar features between oligodendrocyte progenitors and tumor propagating cells in glioma, a concept is supported by expression profiling and mouse models. This talk will review functions for OPCs during development, including proliferation, migration into adult parenchymal tissue and new roles in angiogenesis and vessel co-option. I will discuss provocative similarities between normal OPCs and progenitors for GBM.

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19.02. A common pathway controlling cell migration in normal and neoplastic neural stem cells

Professor Paolo Salomoni - *UCL, UK*

In the central nervous system (CNS), regulation of nuclear function has been implicated in the control of cell cycle and migratory processes during neurogenesis, which serves as the fundamental basis of production/replacement of neurons during development and in the adult brain. Alterations of these processes can lead to neoplastic transformation of neural stem cells (NSCs) and brain cancer. Notably, brain cancer cells use the same routes utilised by neuroblasts/immature neurons and NSCs, suggesting a neurobiological root of brain cancer migration (1). However, our understanding of potentially common mechanisms regulating cell migration/invasion during neurogenesis and brain tumourigenesis remains limited.

Our previous work has implicated the Promyelocytic Leukaemia protein (PML), the essential component of the PML nuclear body (PML-NB), in regulation of embryonic neurogenesis via its ability to control proliferation in NSCs (2,3). We set out to investigate the role of PML in adult neurogenesis and brain cancer. Loss of PML leads to impaired NSC and neuroblast migration and a smaller olfactory bulb in the adult mouse brain. PML controls cell migration via Polycomb Repressive Complex 2-dependent regulation of the Slit2 axon guidance gene independently of its ability to suppress proliferation. A similar epigenetically controlled PML/Slit axis is functional also upon RAS-driven neoplastic transformation of NSCs and in primary GBM cells. Finally, PML correlates with poor overall survival in patients, and its loss impairs tumor invasion in an orthotopic animal model, implicating PML as a potential oncogene in brain tumourigenesis.

Taken together, these findings propose a dual role of PML in regulation of cell fate in the CNS: on one hand it suppresses proliferation, while on the other it promotes cell migration. PML pro-migratory function is retained upon neoplastic transformation,

thus supporting the concept whereby similar mechanisms are at the root of cell migration in both normal and neoplastic cells in the CNS.

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19.03. Exploring the roots of paediatric brain cancers using epigenetic profiling

Dr David Jones - *German Cancer Research Centre (DKFZ), Germany*

Paediatric brain tumors are an extremely diverse collection of different entities, many of which have only recently been (or are still being) discovered thanks to the systematic application of cutting-edge genomics techniques to large sample cohorts. For example, it was recently shown that tumours previously diagnosed under the umbrella term 'primitive neuroectodermal tumor' (PNET) actually comprise a complex group of misdiagnoses of other known entities and well as at least four completely new tumour subtypes (Sturm D et al., Cell 2016). The value of biologically defining these tumour types or subgroups is now also being recognised in the World Health Organisation classification of brain tumours, with molecular groups of medulloblastoma, ependymoma etc. being included for the first time in the revised 2016 edition. Not only do these distinct groups provide valuable clinical clues such as prognostic markers or potential therapeutic targets; they also provide an insight into the complex link between the cellular origins of brain tumours and the susceptibility of these cells to particular genetic aberrations. Epigenetic profiling of brain tumours is particularly valuable in this respect. For example, it is now strongly suspected that the DNA methylation profile of most tumours reflect a 'fingerprint' or memory of the epigenetic state of the particular cell of origin of the tumour subtype. This makes methylation analysis a powerful tool for tumour classification, and for investigating relationships between different entities. Furthermore, mapping of histone marks such as the active enhancer mark H3K27Ac allows for the interrogation of key transcriptional networks defining (tumour) cellular identities, particular through master regulators marked by so-called super-enhancers. My presentation will discuss these principles with examples from some of the latest findings in this area, and their possible implications for diagnostic and therapeutic practice in the future.

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19.04. Epigenetic deregulation in brain cancer

Professor Silvia Marino - *Barts and the London School of Medicine and Dentistry, UK*

Brain cancer is one of the most common causes of cancer-related death in children and adults. Somatic mutations and structural variations that target regulators of epigenetic modifications and chromatin architecture are particularly common in medulloblastoma (MB), the most common malignant brain tumour of childhood and in glioblastoma (GBM), the most aggressive and prevalent adult primary intrinsic brain cancer. The function of these epigenetic alterations is context dependent, but they influence cell identity and cell state transitions during neoplastic transformation and in the hierarchical maintenance of these tumours. They have significantly contributed to the current concept of brain cancer as normal brain development gone awry.

Polycomb group proteins (PcG), highly druggable chromatin modifiers regulating heritable gene repression, are often deregulated in brain cancer. Our previous studies have shown that overexpression of the PcG gene Bmi1 in mouse embryonic neural stem cells increases self-renewal and proliferation without inducing neoplastic transformation. However, repression of BMI1 in patient-derived primary brain cancer cells (MB and GBM) and in mouse models, impairs both self-renewal and proliferation, demonstrating that BMI1 plays a crucial role in tumour maintenance.

Here we will discuss two experimental models generated to elucidate the molecular mechanisms underpinning the role of Bmi1 in brain cancer.

- A genome wide in vivo insertional mutagenesis driven by the Sleeping Beauty transposase in cerebellar glutamatergic progenitor cells engineered to over-express Bmi1 and the molecular convergence with chromatin remodelers leading to the development of medulloblastoma.

- A comparative genome wide transcriptomic and histone modification analysis to dissect the differential downstream cascade mediating the role of Bmi1 in glioblastoma initiating cells as compared to normal neural stem cells.

Funding: Brain Tumour Research Centre of Excellence Award, Medical Research Council UK and Barts Charity

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Symposium 20 – Imaging the emotional brain: fMRI studies in rodents and man
Theme: The neurobiology of stress

20.01. Vulnerability to depression and emotional processing

Dr Stella Chan - *University of Edinburgh, UK*

Depression affects 350 million people worldwide; it is notoriously difficult to treat and highly recurrent. As 50% of depression emerges for the first time in adolescence, the key is to identify risk mechanisms underpinning the early development of this illness, which will ultimately inform the development of preventative interventions. One strong mechanistic candidate is negative biases in emotional processing. While depressed individuals have been shown to be biased towards negative and / or away from positive information, it remains relatively unknown whether this is a cause or consequence of depression. This talk will present findings from three studies examining emotional processing in young people with high risk for depression. The first study examined young never-depressed individuals (mean age 19) with high neuroticism (a robust personality risk factor for depression) and found that neuroticism is associated with negative biases both on behavioural and neural levels. The second study examined cognitive biases in secondary school pupils with dysphoric mood and found particularly large effects on the associations between the emergence of depressive symptoms and negative biases in interpretation of ambiguous scenarios and self-referenced memory processing. The final study is the Scottish Bipolar Family Study, which is a 10 year prospective study examining longitudinal brain changes, both structural and functional, in young individuals with family history of bipolar disorders. Here we found that neural and behavioural biases were apparent in young people with familial risk immediately before and during the emergence of illness. The talk will conclude with a debate around whether these negative biases act as trait vulnerability markers or whether they are triggered by depressive mood and associated stress.

Acknowledgement: These studies received support from The MRC, Stanley Medical Research Institute, Wellcome Trust, Dr Mortimer and Theresa Sackler Foundation, European Union's Seventh Framework Programme and National Health Service (NHS) Research Scotland.

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20.02. Consequences of stress on emotional processing in humans and rodents

Dr Marloes Henckens - *Radboud University, The Netherlands*

Stress exposure exerts a major impact on brain function, influencing several cognitive and affective domains in an attempt to restore homeostasis. Previous work of ourselves and others has indicated that acute stressors trigger a dynamic shift in neural network balance, prompting the reallocation of neural resources to a salience network, promoting fear and vigilance, at the cost of an executive control network. After stress subsides, resource allocation to these two networks reverses, which normalizes emotional reactivity and enhances higher-order cognitive processes important for long-term survival. However, stress-related psychopathology such as major depression and post-traumatic stress disorder, seems to be characterized by a chronic imbalance in network function, favoring emotional vigilance over cognitive control, caused by poor stress recovery. In this talk, both human and rodent behavioural and fMRI data supporting this idea of stress-induced shifts in neural network balance will be presented. Moreover, the talk covers evidence for the long-lasting imbalance in network function that may result from chronic stress exposure or severe trauma in rodents, resembling observations in patients suffering from stress-related disorders. Furthermore, inter-individual differences in stress-sensitivity and -recovery, mediated by differential genetic background or stress hormone release, will be discussed.

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20.03. Stress, oxytocin and vasopressin regulation of emotion: insights from fMRI

Dr Craig Ferris - *Northeastern University, USA*

Functional magnetic resonance imaging (fMRI) in awake animals is used to follow changes in neuronal activity across multiple brain areas coordinating the memories and emotions for particular behaviors. To this end, fMRI in rats is used to identifying the neural circuits of maternal and aggressive behaviors involving oxytocin (OT) and arginine vasopressin (AVP).

Dams are imaged during nursing with and without OT receptor blockade. Central injection of OT stimulates brain activity in areas selective to OT receptor binding and overlap with the same areas activated during pup suckling. OT antagonist suppresses the pattern of brain activation caused by suckling or injected OT. The data suggest OT may strengthen mother-infant bond formation by acting through brain areas involved in regulating olfactory discrimination, emotions and reward [1].

Data from peripheral administration of OT is presented addressing the issue around intranasal OT and changes in prosocial behavior [2]. The results from this imaging study do not support a direct central action of peripheral OT on the brain. Instead, the patterns of brain activity suggest peripheral OT may interact at the level of the olfactory bulb and through sensory afferents from the autonomic nervous system to influence brain activity.

Male rats are imaged for aggressive motivation with and without AVP receptor blockade [3]. To trigger aggressive motivation, male rats were presented with their female cage mate plus a novel male intruder in the magnet during image acquisition. Blocking AVP receptors specifically reduces brain activity involved in aggressive motivation but not sexual motivation.

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Funding: P01HD075750

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20.04. Effects of early-life stress and brain derived neurotrophic factor (BDNF) on emotional processing

Dr Anjanette Harris - *University of Edinburgh, UK*

Stress throughout life, and particularly during early life, associates with increased reactivity to stress and a greater chance of developing affective and cognitive dysfunction during adulthood. Correspondingly, stress alters the architecture of the brain, influencing neuronal growth and survival and dendritic branching, which can have a major impact on the function of neuronal networks. A region that is exceptionally susceptible to the effects of stress and its hormonal mediators (glucocorticoids) is the limbic system (e.g. amygdala, hippocampus), which is responsible for processing emotional and fear related memories. With the recent advent of functional magnetic resonance imaging (fMRI) in rodents comes the ability to determine the nature of the altered processing within brain networks that underpin dysfunctional emotional behaviour. We have used awake rodent fMRI coupled with a fear-conditioning task to determine the effects of early-life stress and glucocorticoid regulated factors, such as brain derived neurotrophic factor (BDNF), on fear circuitry activation (e.g. amygdala) in response to a fear-conditioned stimulus. Early-life stress was found to augment fear circuitry responses to the conditioned stimulus, consistent with previous reports of increased anxiety, depressive-like behaviour and greater stress sensitivity following early-life stress in rats (Brydges et al. 2013). Rats with reduced BDNF, a genetic model of affective disorder and altered emotional processing, displayed impaired fear circuitry activation in response to the conditioned stimulus, supporting a key role for BDNF in the function of the circuitry underpinning emotional learning (Harris et al., 2016).

Funding: Collaborative funding for this research was provided by AbbVie, Center for Cognitive Aging and Cognitive Epidemiology and a Wellcome Trust Institutional Strategic Support Fund. Edinburgh Preclinical Imaging is supported by CCACE and BHF CoRE funds.

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