These papers were presented at the Summer Meeting of the

BRITISH ASSOCIATION FOR PSYCHOPHARMACOLOGY

20 – 23 July, Cambridge, UK

Indemnity

The scientific material presented at this meeting reflects the opinions of the contributing authors and speakers. The British Association for Psychopharmacology accepts no responsibility for the contents of the verbal or any published proceedings of this meeting.

All contributors completed a Declaration of Interests form when submitting their abstract

BAP Office
36 Cambridge Place
Hills Road
Cambridge
CB2 1NS

www.bap.org.uk
Abstract Book 2014

SYMPOSIUM 1
Psycho-immunology (S01-S04)  
A1

SYMPOSIUM 2
Predictors of clinical response in depression (S05-S08)  
A2

SYMPOSIUM 3
ADHD and obesity: Overlapping neurobiology and development of pharmacological treatments (S09-S12)  
A3

SYMPOSIUM 4
Cannabinoids in psychiatry: Current understanding and future treatments (S13-S16)  
A4

SYMPOSIUM 5
Chickens and Eggs: Separating cause and effect in drug addiction (S17-S20)  
A6

SYMPOSIUM 6
Genetic pathways in psychosis: the road to new treatments? (S21-S24)  
A7

SYMPOSIUM 7
The adolescent brain – A key stage in the development of psychiatric disorders? (S25-S28)  
A8

SYMPOSIUM 8
Tobacco addiction in schizophrenia: a translational investigation (S29-S32)  
A9

SYMPOSIUM 9
Dopamine, impulse control disorders and Parkinson’s disease (S33-S36)  
A11

POSTERS

Cognition (Animals) (MA01-MA14)  
A12

Drug Dependence (Human) (MB01-MB28)  
A19

Affective Disorders 1 (MC01-MC28)  
A32

Schizophrenia/Psychosis (Human) (MD01-MD27)  
A46

Anxiety (Nonclinical) (ME01-ME14)  
A59

Neurodegeneration (MF01-MF08)  
A66

Sleep/Pain (MG01-MG04)  
A70
CONTENTS

Eating Disorders (MH01-MH07) A72
Cognition (Humans) (TA01-TA21) A75
Drug Dependence (Animals) (TB01-TB12) A84
Affective Disorders 2 (TC01-TC39) A90
Schizophrenia/Psychosis (Animal) (TD01-TD15) A109
Anxiety (Patients) (TE01-TE09) A116
ADHD/ASD (TF01-TF10) A120

POSTDOCTORAL SYMPOSIUM
Understanding vulnerability for treatment improvement (PD1-PD4) A125

SHORT ORAL PRESENTATIONS

Short Orals 1: Inflammation Insights
See abstracts TC33, TD13, TC36, TE06

Short Orals 2: Understanding Cognition and Emotion
See abstracts TA10, TA11, ME03, TA03

Short Orals 3: Developing Depression
See abstracts TC15, MC03, MC26, MC28

PRIZE WINNER ABSTRACTS (PW1-PW6) A127
S01

IT IS ALL IN THE BODY: MOLECULAR MECHANISMS BY WHICH PERIPHERAL IMMUNE ACTIVATION INDUCES DEPRESSION

Pariante C, Dept of Psychological Medicine, Inst of Psychiatry, Room 2-055, The James Black Centre, 125 Coldharbour Lane, London SE5 9NU, carmine.pariante@kcl.ac.uk

The notion that increased peripheral immune activation may induce depression has developed over the last twenty years, largely as a consequence of two major breakthroughs occurring in the 90s: the experimental evidence using animal models that immune activation leads to behavioural changes resembling depression (sickness behaviour), and the clinical evidence that patients exposed to cytokine therapies for cancers or chronic viral hepatitis develop clinically-significant depression. This initial evidence has been then corroborated by cross-sectional and longitudinal studies that have shown that some depressed patients have increased markers of inflammation, and that increased inflammation in otherwise healthy individuals is a risk factor for the future onset of depression. This talk will offer an historical overview of the evidence supporting the notion that increased peripheral inflammation is on the causal pathway to depression, and will present more recent findings on the molecular mechanisms that are involved in this causal pathway. In particular, this talk will discuss our recent findings, from both experimental and clinical research, showing that increased peripheral inflammation directly affects brain function by reducing hippocampal size, by decreasing neurogenesis and by stimulating the production of neurotoxic and depressogenic metabolites; and that increased peripheral markers of inflammation, both as serum biomarker and as mRNA expression, identifies depressed patients that are less likely to respond to conventional antidepressants, possibly because of a more “developmental” form of depression originating in early life trauma. Finally, this talk will also discuss potential molecular mechanisms by which some antidepressants, including omega-3 fatty acids, have an anti-inflammatory action that could be relevant for their antidepressants effects. In conclusion, twenty years of research on depression and immune system are finally bringing “personalised medicine” right into the core of psychiatry research and patients’ care.

S02

COMPLEMENT AND INNATE IMMUNITY IN ALZHEIMER’S DISEASE - BIOMARKERS, AETIOLOGY AND THERAPEUTIC OPPORTUNITY

Lovestone S, Dept of Translational Neuroscience, Univ of Oxford, Dept of Psychiatry, Warneford Hospital Oxford OX3 7JX simon.lovestone@psych.ox.ac.uk

It has long been recognised from post-mortem studies that inflammation is a component of the pathological process of Alzheimer’s disease and from epidemiological observations that anti-inflammatory drugs reduce risk of dementia. However, the precise inflammatory component has remained elusive, the postulated roles of inflammation as an aetiopathological agent versus a role as an inconsequential bystander has been controversial and trials of anti-inflammatory drugs have proved unsuccessful. However, this is now changing and increasingly research suggests both that it is the complement system that mediates disease and that interventions targeting complement might be a productive therapeutic strategy. Our own research seeking biomarkers for AD strongly implicates the immune system in the pathological process of AD. Using proteomics we and others have shown elements of the complement system including CFH, C3, clusterin and other molecules are consistently altered and are part of a panel we have recently identified that predicts conversion from MCI with a high degree of accuracy. In addition, other elements of the innate immune system including cytokines are unambiguously altered in AD. Evidence that this reflects a primary aetiopathological process comes from genome wide studies which identify complement genes such as CLU and CR1 as important susceptibility factors and where pathway analyses consistently point to the complement system as a mediator of disease. Building on these findings we have conducted a preliminary study using therapeutics designed to target the complement system and early evidence suggests benefits in reducing some aspects of AD pathology in in vivo models.

S03

CHRONIC DISEASE, NEUROINFLAMMATION AND ITS IMPACT ON THE CNS

Perry VH, Centre for Biological Sciences, Univ of Southampton, Mail Point 840, LD80B South Lab and Path Block, Southampton General Hospital SO16 6YD v.h.perry@soton.ac.uk

During progression of a number of neurodegenerative disease such as Alzheimer’s disease, Parkinson’s disease, and prion diseases there is an innate immune response in the brain. This innate immune response is characterised by an increase in the density of the microglia, and their ‘activation’ as judged by alterations in their morphology and the upregulation or de novo synthesis of macrophage antigens. Systemic inflammation can have a profound impact on the phenotype of these microglia that appear to be ‘primed’ by the ongoing neurodegeneration. Proliferation and priming of the microglia is driven at least in part by CSF1, IL-34 via the CSFRI. Systemic inflammation in diverse animal models of chronic neurodegenerative disease leads to exaggerated cytokine synthesis in the brain relative to naïve animals, exaggerated sickness behaviour and acceleration of components of disease progression. Understanding how systemic co-morbidities contribute to progression of chronic neurodegenerative disease offers a route to slowing disease progression and improving the quality of life of those with neurodegenerative disease.
The last 10 years have been a challenging period for development of new drugs for psychiatric disorders, with many companies reducing their levels of investment, despite clear evidence of high levels of unmet need. In this talk, I will briefly rehearse the reasons for the riskiness of drug development in psychiatry and argue that refocusing on immune targets may offer a new way forward that could be more productive than traditional approaches focused on neuronal targets. Specifically, I will address 3 key questions about immunopsychiatry. (1) What is the reason to believe? This will highlight some of the key findings to emerge from the literature that suggest immunological mechanisms could be important in pathogenesis and therapeutics in psychiatry. (2) How will it be different this time? This will point to the potential impact of mechanistically specific and peripherally accessible biomarkers from immunological assays on blood or CSF, and the economic advantages in repurposing anti-inflammatory drugs already in development or marketed for other indications. (3) What will success look like? This will speculate on the potential indications or diagnostic subgroups that might prove to be amenable to immunotherapeutics in psychiatry. I will concentrate on the opportunities to develop anti-inflammatory drugs for treatment-resistant depression.

S05
A CHRONIC SOCIAL STRESS RODENT MODEL OF DEPRESSION
Nephew BC, Cummings School of Veterinary Medicine, Tufts Univ, 200 Westboro Road, North Grafton, MA 01536 USA bcnephew@aol.com

Peripartum depression is one type of mood disorder that is particularly difficult to treat based on several factors: adverse effects of treatments on peripartum offspring development and birth, gender differences in both etiology and treatment responses, unknown effects of perinatal procedures, and an overall lack of data on depression in mothers. Although it is rarely studied compared to depression in males and non-maternal females, it is an ideal target for preventing depression in both genders due to the transgenerational effects of maternal stress and maternal depression. Social stress is a known risk factor for many types of depressive disorders which can be ethologically applied in animals to create clinically relevant transgenerational models. Recent rodent studies using chronic social stress have identified physiological, neurochemical, and neuroimaging markers that support clinical observations in depressed mothers and their offspring, such as estradiol, glucocorticoid receptors, corticosterone, oxytocin, vasopressin, prolactin, ghrelin, and orexin. While these markers represent potential treatment targets, their greatest use may be in the development of preventative measures and practices for peripartum depression, including changes in the rates of current obstetric practices such as birth induction, analgesia, and cesarean section. Discussion of neuroimaging studies using this chronic social stress model will include the identification of transgenerational changes in neural circuits through the use of both resting state functional connectivity and stimulus dependent fMRI. These data will be compared with results from related clinical fMRI data from peripartum depressed patients. The greater use of ethologically relevant animal models of depression combined with clinically relevant manipulations will result in the accelerated development of more effective preventative measures and treatments for depression.

S06
COGNITIVE IMPAIRMENT IN DEPRESSION: IMPLICATIONS FOR TREATMENT
Sahakian BJ, Psychiatry and MRC/Wellcome Trust Behavioural and Clinical Neuroscience Inst, Univ of Cambridge, Box 189, Level E4, Addenbrooke’s Hospital, Cambridge CB2 0QQ
bjjs-sec@medschl.cam.ac.uk

on depression rating scales, although cognition was not assessed (Goss AJ, Kaser M, et al (2013). Modafinil augmentation therapy in unipolar and bipolar depression: A systematic review and meta-analysis of randomized controlled trials. Journal of Clinical Psychiatry, 74(11), 1101-1107). Finally, psychological treatments and cognitive training may enhance cognition by, for example, teaching strategies or reducing negative attentional bias. It may be that combined pharmacological, psychological and cognitive treatments give the best outcome. Cognitive deficits are associated with higher relapse rates and poorer functional outcome. Therefore, cognition in depression is an important target for treatment to ensure good cognitive function, functional outcome (e.g. school, university, work, home life) and wellbeing. Sources of financial sponsorship: Studies by Barbara Sahakian and colleagues on depression and cognitive enhancement with modafinil were funded by the Wellcome Trust and conducted within the MRC/Wellcome Trust Behavioural and Clinical Neuroscience Institute.

S07

NEUROIMAGING-BASED PREDICTORS OF CLINICAL RESPONSE IN DEPRESSION

Fu CH, Psychology, Univ of East London, Water Lane, AE 3.11 London E15 4LZ c.fu@uel.ac.uk

Clinical guidelines offer treatment decision pathways which are of clear benefit to patients and clinicians. A substantive proportion of patients though have illnesses which respond poorly to first line and subsequent treatments. At the present time, biomarkers for predicting clinical response do not exist and are thus not used in day-to-day practice. A prognostic biomarker could point toward the initiation of more intensive or combined therapies at an earlier stage for illnesses that have been identified as being more difficult to treat. In this way, it may be possible to reduce the morbidity associated with potentially multiple, poorly effective treatments. Neuroimaging-based measures of clinical response have demonstrated significant accuracy in predicting clinical response to pharmacotherapy and psychotherapy prior to the initiation of treatment. The potential of functional and structural neuroimaging biomarkers for assisting clinical decisions will be discussed.

S08

MULTIMODAL PROGNOSTIC MARKERS OF COGNITIVE IMPAIRMENT

Ebmeier K, Dept of Psychiatry, Univ of Oxford, Warneford Hospital, Oxford OX3 7JX klaus.ebmeier@psych.ox.ac.uk

Particularly in older age, depression is often associated with cognitive impairment, notably loss of episodic memory and executive function. While cognitive impairment in younger patients may be exclusively due to the depressive disease process, in old age there is some evidence that it represents the brain disease that makes patients vulnerable to developing depressive symptoms for the first time in their lives. Such hypotheses have been examined using case control studies, in particular of older depressed patients with early and late onset of symptoms. A more sensitive and informative approach is the imaging of large random samples (e.g. 800 scans in the Whitehall II Imaging substudy) that includes longitudinal information over the early and mid-adult years and is able to track mood and cognitive function over many decades. Such designs will be able to examine common underlying risk factors for both depression and cognitive impairment and the mediation of one by the other.

S09

PRECLINICAL MODELS OF IMPULSIVITY: PHARMACOLOGICAL AND DIETARY MANIPULATIONS

Robinson ESJ, School of Physiology and Pharmacology, Univ of Bristol, Medical Science Bldg University Walk, Bristol BS8 1TD pmesjr@bris.ac.uk

Animals provide us with the opportunity to study the fundamental neurobiology of behaviour and are invaluable when trying to answer questions about the neurochemical processes involved in normal and pathological behavioural states. In order to translate findings from animal experiments to clinical benefits, a key aspect is the choice of method and how well a given aspect of human behaviour can be replicated in animals. In relation to investigating impulse control, a number of animal tasks exist which allow us to investigate how different neurochemical systems and brain areas are involved regulate different types of impulsive responding. These approaches have been widely used to investigate the neurobiology of ADHD and to investigate how drug treatments act to remediate deficits in impulse control. Deficits in impulse control have been shown to be linked to impulsive action and/or impulsive choice and behavioural tasks for rodents have been developed to facilitate studies into these different types of impairment in response control. Impulsive action can be studied using either the 5-choice serial reaction time task or stop signal reaction time task which are designed to facilitate quantification of waiting versus stopping deficits in rodents respectively. To study impulsive choice, the delayed reward task is used where an animal’s choice for a small immediate reward is compared to selection of a larger but delayed reward. Utilising pharmacological and target brain manipulations, the neural and neurochemical processes which regulate these behaviours have been investigated. The majority of this work has focussed on attention deficit hyperactivity disorder and addiction-related research and may provide important insights into behavioural deficits linked to obesity. This presentation will review the work in this area and discuss what pharmacological studies have revealed about the underlying neurobiology of impulsivity. The talk will also consider how these approaches can be used to understand more about obesity and how deficits in impulse control may contribute to regulation of food intake. Studies using animals to investigate the mechanisms of action of current ADHD medications, including the stimulant drugs methylphenidate and non-stimulant noradrenaline re-uptake inhibitor, atomoxetine will be described. The talk will also describe some of our recent investigations using targeted brain infusions and selective neurochemical lesions, to investigate the loci of effects of atomoxetine. ESJR research is funded by the MRC, BBSRC, NC3Rs and Wellcome Trust.
**S10**

**PHARMACOLOGY OF IMPULSIVITY IN ADHD AND IMPULSE CONTROL DISORDERS**  
ятся S, Dept of Psychiatry, Univ of Cambridge, Box 189, Level E4, Addenbrooke's Hospital, Cambridge, CB2 0QQ srchamb@gmail.com

Background: Impulsivity is a multi-faceted but fruitful construct in psychiatry and clinical neuroscience, broadly defined as a tendency towards behaviour that is inappropriate, unduly thought out, risky, and that leads to unwanted long-term outcomes. Impulsivity is central to the diagnosis of ADHD and patients show elevated rates of substance misuse, criminality, and suicidality. Methods: Selective review of clinical, cognitive, and neurobiological data relating to impulsivity as it manifests in ADHD and in select impulse control disorders. Results: Behavioral and cognitive manifestations of impulsivity cut across multiple disorders including ADHD, substance misuse, trichotillomania, gambling disorder, and obesity. Aberrant structure and function of neural regions including the inferior frontal gyrus, orbitofrontal cortex, and cingulate cortex is implicated. Proof-of-concept pharmacological studies have explored the role of distinct neurochemical systems (noradrenaline, dopamine, serotonin, opioid) in different forms of impulsivity (response inhibition, decision-making, and temporal discounting). Conclusions: Impulsivity is dissociable in neuroanatomical and neurochemical terms, and its measurement has proven valuable in characterising overlap between putatively related disorders. Future work will need to explore whether impulsivity in its various guises can be ameliorated not just in ADHD but also in other related disorders using pro-cognitive agents.

**S11**

**EPIDEMIOLOGY AND CLINICAL PRESENTATION OF ADHD COMORBID WITH OBESITY AND/OR EATING DISORDERS**  
Cortese S, Cambridge and Nottingham, CB5 8JF samuele.cortese@gmail.com

Whilst the comorbidity between ADHD and mood, anxiety and conduct disorders has been extensively studied, the possible association with medical conditions has received less attention. In recent years, an increasing body of empirical research has pointed to a putative association between ADHD and obesity/disrupted eating patterns, although evidence is still in part mixed. In the first part of my talk, I will present the results of a meta-analysis on the prevalence of obesity in individuals with ADHD, both from epidemiological as well as clinical samples (protocol published in Cortese et al., BMJOpen, 2014). I will also present a systematic review of the evidence on the association between ADHD and eating disorders, both in childhood and adulthood. In the second part of the talk, I will discuss how ADHD symptoms may contribute to disrupted eating patterns and obesity, as well as how abnormal eating behaviors may aggravate ADHD symptoms. I will finally present data showing that ADHD is a barrier to a successful treatment of obesity and I will point the importance of screening for and treating ADHD in individuals with obesity.

**S12**

**PHARMACOLOGICAL TREATMENT OF EATING DISORDERS - WHAT CAN WE LEARN FROM ADHD AND OBESITY TREATMENT?**  
Treasure J, Inst of Psychiatry, The Basement, 103 Denmark Hill, London, SE5 8AF janet.treasure@kcl.ac.uk

The appetite system in the brain can be conceptualized as four separate modules; a homeostatic circuit, the homeostatic circuit, memory and learning and self regulation. It is possible that all four of these contribute as causal and maintaining factors for eating disorders. The family and personal history of obesity in bulimia nervosa and binge eating disorders and leanness and poor eating in anorexia nervosa suggest that there may be variation and vulnerability in the homeostatic centre. Food fears may develop from early traumatic experiences (i.e. classical conditioning), others' fears around food (i.e. vicarious learning), or learnt evaluative associations between eating and fatness/stigmatization (e.g. fat talk) and/or non-eating and control/success (e.g. idealisation of thinness). There is evidence of vulnerability factors such as impulsivity and heightened food reward in disorders with loss of control over eating. Furthermore neuroprogressive changes are thought to lead to increased reward sensitivity and changes attentional processes. Cognitive control is depleted by hunger and abnormalities in mood. Treatments can be targeted on all these four domains. For example medication to moderate impulsivity or reward sensitivity such as those used for ADHD or obesity may be of relevance.

**S13**

**RECENT ADVANCES IN OUR UNDERSTANDING OF CANNABINOID PHARMACOLOGY**  
Pertwee RG, School of Medical Sciences, Inst of Medical Sciences, Univ of Aberdeen, Aberdeen AB25 2ZD rgp@abdn.ac.uk

Recent research has identified pharmacological actions of potential therapeutic importance for four non-psychoactive constituents of cannabis: cannabidiol (CBD), cannabidiolic acid (CBDA), cannabigerol (CBG), and Δ9-tetrahydrocannabivarin (THCV). Turning first to CBD and CBDA, recent research has identified pharmacological actions of potential therapeutic importance for four non-psychoactive constituents of cannabis: cannabidiol (CBD), cannabidiolic acid (CBDA), cannabigerol (CBG), and Δ9-tetrahydrocannabivarin (THCV). Turning first to CBD and CBDA, it is noteworthy that (i) the dose-response curves of CBD and CBDA for some of their 5-HT1A receptor-mediated effects are bell shaped, (ii) CBD displays much greater potency than CBD both at enhancing 5-HT1A receptor activation and at reducing vomiting and signs of nausea, and (iii) CBDA can produce some of the latter effects over a broader dose range than CBD. How CBD and CBDA enhance 5-HT1A receptor activation...
remains to be established. Moving on to CBG, it shows significant potency in vitro both as a 5-HT1A receptor antagonist and at producing signs of α2-adrenoceptor activation (Cascio et al., 2010, Br. J. Pharmacol., 159, 129-141). More recently, it has also been found that CBG can (i) produce apparent α2-adrenoceptor-mediated analgesia in a mouse model of inflammatory pain (Comelli et al., 2012, 22nd Annual Symposium on the Cannabinoids, International Cannabinoid Research Society, p.44) and (ii) reduce phencyclidine-induced negative signs of schizophrenia in rats (Gabaglio et al., 2012, First Joint Spanish-Italian Meeting on Cannabinoid Research). Turning finally to THCV, it has been found to activate CB2 receptors as a partial agonist but to block CB1 receptor activation, raising the possibility that it could, for example, ameliorate symptoms of Parkinson’s disease, systemic sclerosis, epilepsy, inflammation and inflammatory pain, obesity, liver damage, stroke, osteoporosis, and nicotine and/or cocaine dependence/relapse. Indeed, preclinical in vivo experiments have already provided supporting evidence for some of these possibilities (Pertwee & Cascio, 2014, Handbook of Cannabis, Oxford University Press, in press). Findings obtained with CBD, CBDA, CBG and THCV in some of these investigations will be described. Supported by GW Pharmaceuticals.

S14

DOES CBD PROTECT AGAINST THE HARMFUL ADDICTIVE, PSYCHOTOMIMETIC AND COGNITIVE EFFECTS OF THC?

Curran V, Clinical Psychopharmacology Unit, University College London, Gower Street, London WC1E 6BT v.curran@ucl.ac.uk. Morgan CJA, Univ of Exeter

The cannabis plant contains a myriad of ingredients we call ‘cannabinoids’. Δ9-tetrahydrocannabinol (THC) is the cannabinoid users seek and what makes them ‘stoned’. Another prominent cannabinoid in many types of cannabis is cannabidiol (CBD) and this appears to have several effects which are opposite to THC. Over the last decade, the level of THC in street cannabis has been increasing whilst the level of CBD has been reduced to almost zero in varieties like ‘skunk’. Over this time period, the number of people who have become dependent on cannabis has also increased so that now 1 in 10 users in Western countries are ‘addicted’. This talk will overview both experimental and naturalistic studies in humans which address the question of how THC and CBD may contribute to determining the acute and chronic effects of cannabis. The focus will be on three major harms: cannabis dependence, psychosis-like effects and cognitive impairment. Funding: UK Medical Research Council

S15

MEDICINAL USES OF THE CANNABIS PLANT

Hazekamp A, Inst of Biology, Leiden Univ, Leiden, The Netherlands ahazekamp@rocketmail.com

The medicinal use of Cannabis is slowly gaining a more general acceptance worldwide. Canada (since 2001) and The Netherlands (since 2003) have government-run programmes, in which quality-controlled herbal cannabis is supplied by specialized and licensed companies. In this presentation a wide review will be given of all aspects of the cannabis plant, its constituents, and their application in medicine and research. All data is based on scientific findings, with special attention for the results obtained through the Dutch medicinal cannabis program over the last years. The presentation will cover topics such as: botanical information and varieties of cannabis; chemical composition; analytical aspects; the endocannabinoid system; pharmaceutical development of natural cannabinoids; clinical trials; and the legal and practical aspects of performing scientific studies. The final goal is to better understand the status quo of cannabis research, and to see the current opportunities for further studies into the medical applications of cannabis.

S16

Cannabinoids as Treatments in Psychiatry: New Developments

Morrison P, The BRC Trials Office M5.06.02, Inst of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF paul.morrison@kcl.ac.uk

The endocannabinoids regulate numerous physiological processes throughout the body and central nervous system. Over the last 25 years the molecular biology of the endocannabinoid system has been revealed in exquisite detail. Endocannabinoids signal via conventional G-protein receptors which makes the system ideal for drug development aimed at therapeutics. Preclinical work suggests that cannabinoid drugs could have been useful in the management of a number of neuropsychiatric conditions including schizophrenia. The first human studies of cannabidiol (CBD) for schizophrenia were encouraging. A number of additional trials of CBD are ongoing, for patients in the early stages of the illness and for those who are treatment resistant. CBD may be particularly useful for patients at high risk of developing schizophrenia, in whom the risks of treatment with dopamine-based antipsychotics probably outweigh any benefits. Another cannabinoid, THCV, may have utility for the metabolic syndrome. Recent animal work has shown that THCV can improve glucose intolerance and insulin sensitivity. The first human studies of THCV have been carried out, and early indications are that THCV is well tolerated. THCV could be beneficial for schizophrenic patients who have suffered metabolic side-effects from their existing treatment regimes.
S17

COGNITIVE DYSFUNCTIONS IN COCAINE USERS ARE PARTLY DRUG-INDUCED BUT REVERSIBLE: EVIDENCE FROM A LONGITUDINAL STUDY

Quednow BB, Dept of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital of the Univ of Zurich, Lenggstr. 31 Zurich, Switzerland 8032 quednow@bli.uzh.ch

Cocaine users consistently display broad cognitive impairments ranging from early attentional processes to complex social cognition. However, it is still unknown whether these impairments are cocaine-induced and if they are reversible. Therefore, we examined the relation between changing intensity of cocaine use and the development of cognitive function within one year. The present data were collected as part of the longitudinal Zurich Cocaine Cognition Study (ZuCo2St). Forty-eight psychostimulant-naïve controls and 57 cocaine users (19 with increased, 19 with decreased, and 19 with unchanged cocaine use) were eligible for analysis. At baseline and after a one-year follow-up, cognitive performance was measured by a comprehensive neuropsychological test battery. Intensity of cocaine use was objectively determined by quantitative six-month hair toxicology at both test sessions. Substantially increased cocaine use within one year (mean +297%) was associated with reduced cognitive performance primarily in working memory. By contrast, decreased cocaine use (-72%) was linked to cognitive improvements in all cognitive domains. Importantly, users who ceased taking cocaine seemed to recover completely, attaining a cognitive performance level similar to that of the control group. However, cognitive recovery was correlated with age-of-onset of cocaine use – early onset users showed hampered recovery. These longitudinal data suggest that cognitive impairment might be partially cocaine-induced but also reversible within one year, at least after moderate exposure and late onset of use. The reversibility indicates that neuroplastic adaptations underlying cognitive changes in cocaine users, which are potentially modifiable in psychotherapeutical or pharmacological interventions. The study was supported by grants from the Swiss National Science Foundation (SNSF; grant No. PP00P1-123516/1 and PP00P1-146326/1) and the Olga Mayenfisch Foundation.

S18

IMPULSIVITY AS A VULNERABILITY FACTOR FOR ADDICTION: A TRANSLATIONAL PERSPECTIVE

Pattij T, Dept Anatomy & Neurosciences, Univ Medical Center, van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands t.pattij@vumc.nl

Impulsivity and drug addiction are closely interrelated in humans, and recent research in animal models has indicated that trait impulsivity may be a predictive factor for addiction liability. In this presentation, data will first be presented demonstrating that distinct forms of impulsive behaviour predict the vulnerability to the onset and motivation to self-administer psychostimulant drugs including nicotine and cocaine in rats. Moreover, in these studies the extinction of and relapse into psychostimulant seeking behavior was also found to be predicted by individual differences in impulsivity. Subsequent neurochemical studies in drug-naive rats have indicated that trait impulsivity is also associated with alterations in dopamine function in corticostriatal brain regions. By contrast, various experiments in our laboratory revealed that volitional self-administration of non-stimulant drugs such as heroin and alcohol was not predicted by distinct forms of impulsive behaviour. Thus, these observations suggest that trait impulsivity primarily predisposes stimulant drug use as opposed to non-stimulants. Secondly, data from pharmacological intervention studies will be highlighted demonstrating that monoaminergic drugs modulating impulsivity have concomitant effects on cocaine self-administration within the same individuals. These experiments are aimed at unraveling whether pharmacological reductions of impulsive behaviour provide novel treatment opportunities for reducing the propensity to self-administer psychostimulant drugs and to promote abstinence.

S19

LOOKING AT THE WHOLE CHICKEN: A SYSTEMIC VIEW OF DRUG ADDICTION.

Ersche KD, Psychiatry, Univ of Cambridge, Brain Mapping Unit, Herchel Smith Bldg Cambridge, CB2 0SZ ke220@cam.ac.uk

Over the years, many different explanations of drug abuse, dependence and addiction have been proposed. One of the most prevailing explanations of addiction is that it is a medical disorder. This disease model has been best summarised by Alan Leshner’s landmark article in Science, in which he argued that chronic drug use leads to significant alterations in the brain that are responsible for the loss of control and other features of addictive behaviour (Leshner AI, 1997, Science 278:45-47). Indeed, much evidence has been accumulated from neuroimaging studies in drug-dependent individuals linking abnormalities in brain structure and function with addictive symptoms. However, this ‘exposure model’ of addiction is not the whole picture, and has been challenged by longitudinal and endophenotype studies showing that impulsive and compulsive behaviours are likely to have pre-dated drug-taking and potentially predisposed individuals towards the development of addiction. Although examining the research evidence in light of the exposure and the susceptibility models of addiction is important, in my talk, I would like to put the spotlight on another side of drug addiction, namely the effects that addictive drugs exert on peripheral systems such as the immune system. I will argue that drug addiction is not merely a brain disease, but a systemic illness. Infectious diseases are the most common and costly side effects of drug addiction. It is generally assumed that the increased rate of infections in drug-dependent individuals is due to risky behaviours such as sharing pipes and needles, and to more regular exposure to disease-related pathogens. However, evidence is now emerging suggesting that the immunomodulatory effects of addictive drugs, including cocaine, may account for the high infection risk seen in chronic drug users, making them more susceptible to contracting infectious diseases. Disruptions in immunity may also underlie the cognitive-emotional dysfunction typically seen in drug-dependent individuals; co-morbid conditions that are currently difficult to treat in these patients. Looking beyond chickens and eggs and taking a more holistic approach towards drug addiction may be critical if we are to develop more effective treatments to improve the quality of life for individuals affected by drug addiction. KD Ersche is supported by the Medical Research Council and has no conflict of interest.
S20

VULNERABILITY TO ADDICTIONS: DOPAMINE STUDIES IN HUMANS

Leyton M, Psychiatry, McGill Univ, 1033 Pine Ave W Montreal, QC, H3A1A1 marco.leyton@mcgill.ca

Background: Animal studies suggest that dopamine neurotransmission influences responses to reward-related stimuli and susceptibility to drug-seeking behavior. The relevance of this work for humans, though, has been unclear. Methods: During the past 15 years, we have conducted a series of studies using positron emission tomography (PET) and acute phenylalanine/tyrosine depletion (APTD) to measure dopamine release and investigate its behavioral significance. Results: The studies suggest that, in humans, abused drugs, across multiple pharmacological classes, increase extracellular dopamine levels. With repeated drug administration, these dopamine responses can become progressively greater (sensitized) and conditioned to environmental cues. Diminishing the drug-induced dopamine responses does not alter the substances’ pleasurable effects or change the self-administration of easily available drugs. Decreasing dopamine transmission does however reduce the propensity to respond preferentially to rewards, the willingness to sustain effort to obtain rewards (alcohol, cigarettes, money), and corticol-abfrontal functional connectivity. In people at elevated risk for addictions, dopamine responses to addictive drugs are markedly altered, differences that remain after controlling for past drug use. Discussion: Together, these studies might identify more closely the specific role of dopamine in reward-seeking behaviors. Dysregulated dopamine responsibility might constitute a vulnerability trait for addictions. Funding from the Canadian Institutes of Health Research (CIHR)

S21

THE PROMISE OF USING HUMAN INDUCED PLURIPOTENT STEM CELLS IN SCHIZOPHRENIA

Brennand KJ, Psychiatry, Mount Sinai School of Medicine, 1425 Madison Ave, 9-20B, 10025, USA kristen.brennand@msm.edu

Brennand Ka,b,c, Savas JNe, Kim Ya, Tran Na,b,c, Simone Aa, Hashimoto-Torii Kf,g, Beaumont Kf,h, Kim HJa, Topol Ab,c, Ladransf,b,c, Abdelrahim Mb,c, Matikainen-Ankney Bc, Chao S-hi, Mrkisch Mh, Rakic Pf, Fang GD, Zhang Bd, Yates III JRe, Gage FHf, 1 a Salk Inst for Biological Studies, Lab of Genetics, 10010 North Torrey Pines Road, La Jolla CA 92037 b Current address: Dept of Psychiatry, Icahn School of Medicine at Mount Sinai, 1425 Madison Avenue, New York, NY 10029 c Dept of Neuroscience, Icahn School of Medicine at Mount Sinai, 1425 Madison Avenue, New York, NY 10029 d Depts of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, 1425 Madison Avenue, New York, NY 10029 e Dept of Chemical Physiology, The Scripps Res Inst, 10550 North Torrey Pines Rd. La Jolla, CA 92037 f Dept of Neurobiology and Kavl Inst for Neuroscience, Yale Univ School of Medicine, New Haven, CT 06510, USA g Center for Neuroscience Research, Children’s National Medical Center, Washington DC 20010 h Depts of Chemistry and Biomedical Engineering, Northwestern Univ, Evanston, IL 60208 I Center for Biosignatures Discovery Automation, Biosign Inst, Arizona State Univ Tempe, AZ 85287

Schizophrenia (SZ) is a debilitating neurological disorder. Though postmortem studies have revealed reduced neuron size and spine density in SZ brain tissue, the molecular mechanisms underlying the disease state remain unclear. We directly reprogrammed fibroblasts from SZ patients into human induced pluripotent stem cells (hiPSCs) and subsequently differentiated these disorder-specific hiPSCs into neurons; SZ hiPSC neurons showed diminished neuronal connectivity, which could be ameliorated following treatment with the antipsychotic Loxapine. Gene expression comparisons of our hiPSC-derived neural progenitor cells (NPCs) and 6-week-old neurons to the Allen BrainSpan Atlas indicate that our hiPSC neural cells, from controls and patients with schizophrenia (SZ), most resemble fetal rather than adult brain tissue, indicating that hiPSC-based models may not yet be suited for the study of the late features of this disorder. Because much of the gene signature of SZ hiPSC-derived neurons is conserved in NPCs, we used two independent discovery-based genome-wide approaches - microarray gene expression and stable isotope labeling by amino acids in cell culture (SILAC) quantitative mass spectrometry analyses – to identify cellular phenotypes in SZ hiPSC NPCs from four SZ patients. From our findings that SZ hiPSC NPCs show abnormal gene expression and protein levels related to neural migration and oxidative stress, we predicted, and subsequently observed, aberrant migration and increased oxidative stress in SZ hiPSC NPCs. This platform, consisting of reproducible phenotypes identified through scalable assays, can be applied to expanded cohorts of SZ patients, making it a potentially valuable tool with which to study the developmental mechanisms contributing to abnormal neuronal connectivity and synaptic function seen in SZ.

S22

THE IMPACT OF SCHIZOPHRENIA RISK GENES UPON BRAIN FUNCTION

Lawrie S, Division of Psychiatry, Univ of Edinburgh, Kennedy Tower, Royal Edinburgh Hospital, Edinburgh, EH10 5HF s.lawrie@ed.ac.uk

In the past four decades or so it has become clear that schizophrenia is highly heritable and that it is associated with structural and functional neuroimaging abnormalities, which are themselves heritable. In recent years, several genetic risk variants have been identified for schizophrenia but very few if any of these are specific, raising important questions about how risk might be translated into disorder and indeed how we classify disorders in the first place. We, and several other research groups, have shown significant impacts of some common risk variants and pooled estimates of aggregate genetic liability (‘polygenic risk’) on the organisation and activity of structural and functional pathways in the brain. Rare risk genotypes (DISC1, 22q11 and other CNVs) have also been shown to disrupt these processes in both human and animal imaging experiments. Neuroimaging collaborations across Europe and the rest of the world have been able to identify novel genetic variants that impact upon the brain, and imaging is poised to have an impact in clinical practice, at least in terms of earlier diagnosis. Predicting treatment response to antipsychotic treatment with genetic and/or imaging markers is however, at least as yet, largely aspirational. Realising this aim is likely to require animal studies with existing and novel compounds, as well as human studies with sufficient power to map gene*gene and gene*environmental interactions (to quantify risk), genetic imaging studies as part of clinical trials(to quantify therapeutic effects), and genetic/imaging stratification approaches (to identify sub-groups for particular approaches).
S23

TRANSLATING THE SCHIZOPHRENIA GENOME

Brandon NJ, Neuroscience iMED, AstraZeneca, 141 Portland St, Cambridge, MA 02421, USA nick.brandon@azneuro.com

The struggles of developing new drugs for mental illness are well documented. In recent years we have seen little success in progressing new molecules and mechanisms through clinical success in populations which desperately need alternatives to current treatments. There are multiple reasons highlighted as potential explanations for the failure, ranging from non-predictability of animal models to the (lack of) selection of patients for trials. The failure (to date) of the mGluR2/3 and PDE10A inhibitor mechanisms is a good example to bring out the issues with the historical drug discovery path. In parallel with this perceived failure, our basic knowledge of the genetics and circuitry of these disorders has increased dramatically. The genetic data emerging from groups such as the Psychiatric Genomic Consortium (PGC) is providing a rich source of potential insights and pathways for drug discovery. How as a field are we going to convert these apparent riches into medicines which really make a difference to patients? There are likely a number of strategies we can take. I will focus on 2 approaches we have taken. Though not identified in contemporary genetic studies, I will focus on the risk factor Disrupted in Schizophrenia 1 (DISC1) to try and provide insight into approaches and pitfalls for understanding the biology and relevance of a genetic finding. Then I will introduce the recent efforts in our group which have started to try and combine advances in iPSC cell biology and brain circuitry to drive new target identification, validation and translation.

S24

UNDERSTANDING THE GENETIC BASIS OF PSYCHIATRIC DISORDERS. BEYOND DESCRIPTIVE SYNDROMES TO SHARED BIOLOGICAL PATHWAYS

Breen G, MRC SGDP Centre, Inst of Psychiatry, King’s College London, SE5 8AF gerome.breen@gmail.com

Genome-wide association (GWAS) studies of psychiatric disorders have identified multiple variants, many of which show phenotypic pleiotropy. We (the Psychiatric Genomics Consortium Pathway Analysis Subgroup) use a pathway analysis approach integrating multiple methods on data of >60,000 participants from Phase 1 of the Psychiatric Genomics Consortium (PGC): autism spectrum disorder (ASD), attention deficit-hyperactivity disorder (ADHD), bipolar disorder (BIP), major depressive disorder (MDD), and schizophrenia (SCZ). Our analyses clearly indicate a shared etiology of three adult onset psychiatric disorders, BIP, MDD, and SCZ, at the pathway level (p<1x10-3) with histone methylation pathways showed significant association (p=1.08x10-8) as well as multiple immune processes. Aberrant gene expression of histone methylation pathway genes may be a common etiologic mechanism underlying adult psychiatric disorders. We confirm a role of calcium channel signaling genes, immune pathways and postsynaptic density in psychiatric disorders. We also note the strong evidence for a role of GSK3-β, β-Catenin and WNT mediated signaling in Bipolar Disorder and protein phosphatase 2a activity in major depression. Many of the pathways identified have well defined pharmacology and hold promise for further functional and pharmacological experiments.

S25

RISK TAKING AND THE SOCIAL BRAIN IN ADOLESCENCE

Blakemore S-J, Inst of Cognitive Neuroscience, University College London, 17 Queen Square, London, WC1N 3AR s.blakemore@ucl.ac.uk

Adolescence is a period of formative biological and social transition. Social cognitive processes involved in navigating an increasingly complex social world continue to develop throughout adolescence. Areas of the social brain undergo both structural changes and functional reorganisation during the second decade of life, and this possibly reflects a sensitive period for adapting to one’s social environment. The changes in social environment that occur during adolescence might interact with increasing executive functions and heightened social sensitivity to influence a number of adolescent behaviours. I will discuss the importance of considering the social environment and social rewards in adolescent cognition and behaviour.

S26

ANOREXIA NERVOSA, COGNITION AND ESTROGEN: ONE HARDWORKING HORMONE

Katzman D, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada, M5G 1X8 debra.katzman@sickkids.ca

Anorexia nervosa (AN) is a severe eating disorder that typically begins during adolescence. Chronic starvation associated with AN results in medical complications that affect every organ system in the body. In adolescent-onset AN, a particularly concerning complication involves abnormalities in brain structure and cognitive function. Dynamic structural brain changes and cognitive maturation that occur during adolescence may be compromised by AN with long-term consequences. Cognitive deficits may also hinder treatment efforts and contribute to illness chronicity. Little is known about cognition in adolescent with AN. Abnormalities in cognitive function have been reported in acutely ill adolescents with anorexia nervosa. Some studies have found that these abnormalities persist, while others have found that they are reversible in the context of “recovery”. Although weight is one indicator of biological recovery from AN, menstrual function may remain abnormal in some weight-recovered patients. This presentation will review the relationship between menstrual function and cognitive performance in AN, highlighting the possibility that weight and menstrual function may have independent effects on brain structure and cognitive function in AN. Possible mechanisms underlying neural and cognitive deficits with AN will be discussed.
S27

DEPRESSION AND CONDUCT DISORDERS AND THE HUMAN ADOLESCENT BRAIN

Goodyer IM, Psychiatry, Univ of Cambridge, Douglas House, 18b Trumpington Road, Cambridge, CB2 8AH ig104@cam.ac.uk

Over the past 2 decades the imaging sciences have provided the tools for estimating structural and functional differences in the brain between those with mental illnesses and well controls. I will describe our imaging studies that investigated the neuroscientific bases of the developmental taxonomic theory of conduct disorder in adolescents (Passamonti L et al (2010) Arch Gen Psychiatry. 67(7):729-38 ; Fairchild G, et al (2011) American Journal of Psychiatry. 168(6):624-33). Subsequently I will describe the ongoing work in revealing neurocognitive deficits associated with first episode unipolar depressions in 11 to 17 year olds (Graham J, et al (2013) Journal of Affective Disorders 151(2):423-31). Finally I will discuss the importance of taking age and the impact of adverse environments into account to understand the putative effects of metal illness on the developing brain (Walsh ND, et al (2012) Neuroimage 15; 63(3):1670-80 ; Walsh ND.,et al (2014) NeuroImage: Clinical , 4: 308–318 ; Moutsiana et al (2014) Journal of Child Psychology and Psychiatry doi: 10.1111/jcpp.12198. [Epub ahead of print]). Overall mental illnesses may share a core set of neural characteristics that are associated with elevated general risks for any psychopathology and a set of specific deficits that may relate to a specific patterning of symptoms. This work was supported by a project grant from the MRC, a trials grant from NIHR and project , programme and strategic awards from the Wellcome Trust. Additional support was provided by the Friends or Peterhouse. The work was hosted and completed within the Cambridge and Peterborough NHS Foundation Trust.

S28

ADOLESCENCE, GONADAL HORMONES AND ANXIETY-LIKE BEHAVIOUR IN RODENTS

Brown GR, School of Psychology & Neuroscience, Univ of St Andrews, South Street, St Andrews, Fife KY16 9JP, grb4@st-andrews.ac.uk

Introduction: In human beings, sex differences in susceptibility to mood and anxiety disorders emerge during adolescence, with females exhibiting greater susceptibility than males. This sex differences in adolescent susceptibility is thought to be influenced by peri-pubertal fluctuations in gonadal hormones, with fluctuations in ovarian hormones enhancing susceptibility in females, and testicular hormones providing protective effects in males. The hypothalamic-pituitary-gonadal axis is known to interact closely with the developing stress hormone axis during adolescence, and sex differences in exposure to gonadal hormones could have long-term implications for stress reactivity. However, the exact mechanisms that underlie sex difference in susceptibility to mood and anxiety disorders are not fully understood. Methods: In a series of studies on laboratory rats, we examined the emergence of sex differences in anxiety-like behaviour during adolescence, and we experimentally manipulated gonadal hormone levels during adolescence and examined the immediate and long-term effects on anxiety-like and social behaviour and on hormone receptor gene expression in the brain. Gonadal hormones were suppressed either by using a gonadotrophin-releasing hormone (GnRH) antagonist (Antide) or by surgical gonadectomies. Results: The results showed that adolescent exposure of male rats to testicular hormones influenced response to novelty and male-typical social interactions in both adolescence and adulthood; for instance, suppression of adolescent gonadal hormone levels reduced rough-and-tumble play and preference for novel objects in adolescent males, while males that had been castrated before adolescence (i.e., not exposed to testicular hormones during adolescence) were more exploratory in novel environments and interacted less with female social partners than males that had been castrated at the end of adolescence. In contrast, manipulating gonadal hormones in adolescent females had relatively little impact on behavioural development. Conclusions: These results provide support for the hypothesis that adolescence is a sensitive period of life, during which exposure to testicular hormones has both 'activational' and 'organisational' effects on behaviour. Sex differences in social, exploratory and risk-taking behaviour emerge during adolescence in rats, and these behavioural changes are influenced by gonadal hormones. In particular, exposure of male rats to testicular hormones had both immediate and long-term impact on behavioural development. Future studies that elucidate the actions of gonadal hormones on the developing adolescent brain will potentially increase our understanding of sex differences in susceptibility to a range of neuropsychological disorders.

S29

NICOTINIC RECEPTOR MODULATION OF CORTICAL NETWORKS IN RODENT AND HUMAN BRAIN

Mansvelder H, Head, Dept of Integrative Neurophysiology, CNCR, Neuroscience Campus Amsterdam, VU University Amsterdam, De Boelelaan 1085, Room C-440, 1081 HV Amsterdam , The Netherlands h.d.mansvelder@vu.nl

The prefrontal cortex (PFC) is the main link in integrating emotional and motivational state to regulate top-down attentional processes. Acetylcholine modulates PFC neuronal networks by activating nicotinic acetylcholine receptors (nAChRs) to support attention. However, how neuronal activity changes in the PFC during attention and which nAChR subtypes mediate this is only rudimentarily understood, but progress is being made. Recently, exciting new insights were obtained in the dynamics of cholinergic signaling in the PFC and modes of acetylcholine transmission via nAChRs in the neocortex. Here, I will discuss how different subtypes of nAChRs expressed by distinct types of neurons regulate PFC function in rodent and human brain. In addition, I will discuss how low concentrations of nicotine, as experienced by smokers, interfere with cholinergic signaling depending on the type of nAChR subunit expressed. HDI is funded by the Netherlands Organization for Scientific Research (NWO VICI grant), European Research Council (ERC StG “BrainSignals”), the Dutch Fund for Economic Structure Reinforcement (FES, 0908 “NeuroBasic PharmaPhenomics project”), the European Union 7th Framework Programme (HEALTH-F2-2009-242167 “SynSys”), and the Human Brain Project.
S30
LOOKING BEYOND PRIMARY REINFORCEMENT TO EXAMINE SELF-MEDICATION OF NICOTINE IN SCHIZOPHRENIA: USE OF CONCURRENT CHOICE PROCEDURES FOLLOWING SUB CHRONIC KETAMINE EXPOSURE IN RATS
Shoaib M, Inst of Neuroscience, Newcastle Univ, Newcastle, NE2 4HH mohammed.shoaib@newcastle.ac.uk

Cognitive deficits represent one of the core disabling symptoms within this disorder, accountable for the majority of disruption to everyday life. Over 80% of patients with schizophrenia smoke compared to just 30% of the general population, which has been postulated as a form of self-medication to remediate the cognitive symptoms. Our laboratory has shown that a sub-chronic, sub-anaesthetic dosing regimen of the NMDA antagonist ketamine can induce cognitive deficits on a variety of cognitive domains such as memory capacity of working memory and executive decision-making in the attentional set-shifting task. The objective was to examine the effects of treating rats with ketamine (daily injection of 30mg/kg IP for 5 days) on acquisition to self-administer intravenous nicotine (0.015 & 0.03mg/kg/inj) using two-lever operant conditioning chambers. Following 5 days of a ‘washout’ period from the sub-chronic treatment, groups of rats (n=12) were given access to intravenous nicotine in 1 hr sessions under a fixed-ratio schedule of reinforcement. Both ketamine- and vehicle-treated subjects showed steady rates of acquisition with no significant difference between the treated groups. Differences were however apparent when rats were presented a choice between nicotine and sucrose (0.2ml of 5mg/ml solution) under a concurrent choice procedure (VR4). Over 3 three concurrent sessions, vehicle-treated rats migrated their responses exclusively to the sucrose lever, whilst ketamine-treated rats were resistant and made fewer responses on the sucrose lever but more importantly maintained their intake of nicotine. The results from this experiment suggest that the sub-chronic ketamine regimen used to model cognitive deficits associated with schizophrenia does not modify the primary reinforcing effects of nicotine. However, within value-based decision making in nicotine addiction, ketamine exposure made rats resistant to non-drug alternative reinforcers such as sucrose. These findings suggest that the high prevalence of tobacco smoking amongst people diagnosed with schizophrenia may represent self-medication in order to restore cognitive deficits, rather than an increase in their subjective feeling of satisfaction from the nicotine. (Research supported by Newcastle University UK)

S31
THE TOBACCO ABSTINENCE SYNDROME AND ITS MODULATION BY THE Α4Β2 NICOTINIC PARTIAL AGONIST VARENCLINE IN SCHIZOPHRENIA VERSUS CONTROL SMOKERS
Wing VC, Faculty of Medicine, Imperial College London, Hammersmith Hospital, Du Cane Road, London W12 0HS victoria.wing13@imperial.ac.uk

Background: As well as being more likely to smoke, patients with schizophrenia have more difficulty maintaining abstinence than the general population. This may be in part due to a more severe tobacco abstinence syndrome involving craving, withdrawal and cognitive impairment (e.g., working memory dysfunction). Varenclinc tartrate (Chantix®), a α4β2 nicotinic partial agonist, is a smoking cessation medication with efficacy in smokers with schizophrenia. However, it is not known if its anti-craving and pro-cognitive effects reported in healthy smokers extend to those with schizophrenia. This human laboratory study is a systematic comparison of varenclinc in schizophrenia and control smokers which could provide important information about mechanisms of smoking cessation in different groups. Methods: We evaluated the acute tobacco abstinence syndrome and the effects of varenclinc treatment in schizophrenia (n=14) and control (n=14) smokers. A within-subject design was used to evaluate the effects of three doses of varenclinc (0, 1 and 2 mg/day x 3 days administered in a counterbalanced sequence over three separate test weeks). The three day laboratory paradigm included three smoking conditions: 1) smoking as usual, 2) after overnight abstinence and 3) after reinstatement of smoking. The laboratory sessions including smoking topography, self-reported craving and withdrawal measures and a cognitive battery (sensorimotor gating, attention, processing speed, visuospatial working memory, verbal learning and memory and impulsivity). Results: Overnight abstinence increased craving in both control and schizophrenia smokers; varenclinc attenuated the abstinence-induced increases in both groups with some limited evidence for more robust effects in control smokers. In contrast, abstinence-induced deficits in cognition, particularly in the domain of visuospatial working memory, were only observed in the schizophrenia group. Sub-chronic varenclinc (1 mg/day) was able to fully attenuate this abstinence-induced cognitive impairment. Varenclinc had no effects on cognitive function in the control smokers. Conclusions: This study adds to the growing body of evidence that the tobacco abstinence syndrome is associated with specific cognitive deficits in schizophrenia. Varenclinc reduced craving in both groups but in schizophrenia had the additional benefit of blocking abstinence-induced cognitive impairments. These data indicate that α4β2 nicotinic partial agonists may be promising treatments for tobacco dependence and cognitive enhancement in schizophrenia. We are currently exploring if differences in the tobacco abstinence syndrome are associated with relapse susceptibility and if varenclinc can modulate this relationship. Preliminary genetic and brain imaging data examining the role of cortical dopamine in the tobacco abstinence syndrome in schizophrenia will also be discussed. Funding Disclosure: Ontario Mental Health Foundation (OMHF) Operating Grant, Pfizer Investigator Initiated Research (IIR) Award, Pfizer Global Research Award for Nicotine Dependence (GRAND)

S32
BRAIN CIRCUITS THAT LINK SCHIZOPHRENIA TO HIGH RISK OF CIGARETTE SMOKING
Hong E, Maryland Psychiatric Research Center, Univ of Maryland School of Medicine, 55 Wade Avenue, Baltimore, MD 21228, USA ehong@mprc.umaryland.edu

Introduction: Rates of tobacco smoking are elevated in individuals who suffer from mental illness, and are highest in schizophrenia, about three-to-four fold higher than the smoking rate of the U.S. population. Schizophrenia is associated with excess mortality, with smoking-related illnesses being the number one cause of preventable mortality. The link between smoking and mental illness is well established epidemiologically, but its biological
basis remains unknown. Current conceptualization of schizophrenia-nicotine addiction comorbidity centers on smoking as self-medication to overcome neurocognitive deficits and/or temper side effects of antipsychotic medication. While these factors likely contribute to the high prevalence of smoking in schizophrenia, many individuals at risk for schizophrenia smoke prior to disease onset. Therefore, increased risk of smoking in schizophrenia may not be entirely due to environmental or neuroleptic medication effects and may instead be due to a shared neurobiological path. Methods: Resting state functional magnetic resonance imaging (fMRI) was performed using the dorsal anterior cingulate (dACC) as a seed region in smoking and nonsmoking patients with schizophrenia (n = 54), matched controls (n = 65), and nonpsychotic first-degree relatives (n = 24). Results: Schizophrenia is associated with reduced connectivity between anterior cingulate – subcortical limbic regions. Similarly reduced circuit connectivity strength is also present in smokers without schizophrenia, and in people with schizophrenia without smoking, suggesting that this circuit abnormality in schizophrenia is overlapped with one of the same circuits associated with risk for smoking. Conclusions: Based on these findings, we think that individuals with schizophrenia are predisposed to smoking due to abnormalities inherent to schizophrenia in the anterior cingulate-right limbic circuits associated with nicotine addiction. Results of this study support a shared brain circuit theory to explain the high risk of smoking in schizophrenia. Our findings may establish a biologically defined brain circuit mechanism that contributes to the high prevalence of smoking.

S33
DOPAMINE AND IMPULSIVITY: ANIMAL MODELS
Dalley JW, Psychology, Univ of Cambridge, Downing St, Cambridge CB2 3EB jwd20@cam.ac.uk

Introduction: Pathological forms of impulsivity are present in a number of neuropsychiatric and neurological disorders including attention-deficit hyperactivity disorder (ADHD), addiction, and Parkinson’s disease (PD). Over the last 3 decades research in experimental animals has successfully mapped the major neural loci underlying the expression and modulation of different subtypes of impulsive behaviour. This talk will focus critically on the widely acknowledged role of dopamine in impulsivity, especially within the mesolimbic system, and considers whether dopaminergic mechanisms alone are sufficient to account for all forms of impulsive behaviour. Methods: The translational utility of several animal models of impulsivity will be discussed, including the selection of highly impulsive rats on a five-choice serial reaction time task, which show persistent failures to suppress anticipatory responses for future rewards. The neural mechanisms of impulsivity will be surveyed and integrated with recent data obtained using positron-emission tomography, magnetic resonance imaging, in-vivo neurophysiology, ex-vivo autoradiography, and brain protein chemistry. Results: High-impulsive rats show (1) reduced D2 receptor availability in the ventral striatum lateralised to the left hemisphere; (2) exaggerated gamma oscillatory activity (50-60 Hz) and impoverished dopamine-modulated delta activity (2-5 Hz) in the prefrontal cortex and nucleus accumbens; (3) decreased glutamate decarboxylase expression in the nucleus accumbens core accompanied by reduced dendritic spine markers; and (4) reduced GABA(A) receptors in the anterior cingulate cortex. Conclusions: A burgeoning body of evidence now suggests that impaired dopaminergic signalling is unlikely to explain all aspects of impulsive behaviour in animal models, particularly when expressed as a trait-like marker. Nevertheless, dopaminergic drugs that increase impulsivity in experimental animals are also associated with the development of impulse control disorders in PD. Using evidence derived from neuropsychopharmacological studies in rodents the putative dependence of this effect on dopaminergic mechanisms will be discussed. Supported by the UK Medical Research Council and Wellcome Trust.

S34
DOPAMINE AND IMPULSIVITY: COMPUTATIONAL MODELS
Daw ND, Center for Neural Science & Dept of Psychology, New York Univ, 4 Washington Pl Rm 809, New York 10003, USA daw@cns.nyu.edu

Dopamine plays multiple roles in the brain, more than one of which may contribute to its role in impulsivity. I discuss computational models of different aspects of dopaminergic function and our experimental work testing these models. In particular, dopamine in different parts of striatum is widely hypothesized to serve as a reinforcement signal for habit learning, but also in invigorating or energizing the expression of previously learned behaviors, as in Pavlovian-instrumental transfer. I review how the categories of Pavlovian, goal-directed, and habitual behavior have been conceptualized in terms of computational models of reinforcement learning and how these theories, in turn, have been used in laboratory experiments to help to dissociate these processes and their neural substrates, especially in humans. This work has shed particular light on interactions between Pavlovian and instrumental, and habitual and goal-directed, processes, and the nature of these interactions may clarify dopamine’s roles in pathological (and normal) impulsivity.

S35
DOPAMINE, IMPULSE CONTROL DISORDERS AND PARKINSON’S DISEASE: PET IMAGING STUDIES
Piccini P, Centre of Neuroinflammation and Neurodegeneration, Imperial College, Block B, Hammersmith Hospital, Du Cane Road, London W12 0HS paola.piccini@imperial.ac.uk

Impulsive-compulsive behaviours (ICBs) are an increasingly well-recognised adverse-effect of dopaminergic medications used to treat Parkinson’s disease (PD). ICBs include the DSM-IV impulse control disorder (ICD) pathological gambling, plus the putative ICDs compulsive sexual behaviour, compulsive buying, and binge eating, together with punding and the addiction-like compulsive use of dopamine replacement therapy, or dopamine dysregulation syndrome (DDS). In vivo molecular imaging studies using single photon emission computed tomography (SPECT), and positron emission tomography (PET) have provided valuable insight into the neuroanatomy and neurobiology involved in the development of ICBs. Our group was the first to conduct a study using PET and [11C]-raclopride, a tracer that specifically binds to D2 receptors, to image dopaminergic function in patients with DDS compared with PD control patients. A two-scan PET protocol was used to calculate dopamine release following an oral dose of levodopa. We found that individuals with DDS showed an enhanced ventral striatal release of dopamine to levodopa, which was correlated
with increased motivation to take the drug. This finding was consistent with the incentive sensitization theory of compulsive drug use, which posits that compulsive drug use arises from the excessive attribution of incentive salience or “wanting” for drug rewards and their cues, due to progressive neuroadaptations in dopamine projections to ventral striatal motivation circuits. Subsequently, a study assessing PD patients with pathological gambling performing a simulated gambling task also found exaggerated ventral striatum dopamine-release in pathological gamblers versus control PD patients. A more recent study from our group used visual cues to investigate dopamine release in the striatum of PD with different ICDs. We showed that medicated PD with ICBs exhibit greater decrease in ventral striatum [11C]-Raclopride binding (i.e. enhanced dopamine release), than PD controls patients following exposure to a variety of reward-related cues, but not to levodopa challenge alone. The heightened response of striatal reward circuitry to heterogeneous reward-related visual cues amongst a group of patients with different ICDs is consistent with a global sensitization to appetitive behaviour with dopaminergic therapy in vulnerable individuals. The talk aims to give an overview of these data and to discuss their respective roles in PD with ICDs.

**S36**

**DOPAMINE, IMPULSE CONTROL DISORDERS AND PARKINSON’S DISEASE: COGNITIVE AND FUNCTIONAL IMAGING STUDIES**

Voorn V, Dept of Psychiatry, Univ of Cambridge, Downing Street, Cambridge CB0 0QQ vv247@cam.ac.uk

Dopamine agonists are associated with Impulse control disorders (ICDs) in Parkinson’s disease. These behaviours include pathological gambling, compulsive shopping, compulsive sexual behaviours and binge eating and can be associated with marked financial and social consequences. The pathophysiology underlying this relationship between dopamine agonists and ICDs are believed to be an interaction between an underlying individual susceptibility, medications and possibly Parkinson’s disease. This talk focuses on underlying impairments in cognitive measures and functional imaging studies in the context of theories of addiction. Impairments in decisional impulsivity including enhanced delay discounting, reflection impulsivity and risk taking along with working memory deficits have been consistently observed. Enhanced novelty seeking and delay discounting appears to differentiate the externalizing and internalizing behaviours. Imaging studies suggest enhanced ventral striatal dopamine release and activity to cues, gambling and reward anticipation and outcomes, along with decreased orbitofrontal activity consistent with impairments in behavioural controls. Understanding these behaviours provides insight into ICDs in the general population and the role of dopamine on behavioural control.

**MA01**

**ENDOGENOUS NEUROSTEROIDS ACT AS POSITIVE ALLOSTERIC MODULATORS OF THE NMDA RECEPTOR**

Brazaitis CT, School of Psychology and Neuroscience, Univ of St Andrews, St Mary’s College, South St, St Andrews, Fife KY16 9JP ctb9@st-andrews.ac.uk

Cooper MA(1), Belelli D(1), Hamilton N(2), Brown VJ(3), Lambert JJ(1) (1) Div of Neuroscience, Medical Research Inst, Ninewells Hospital & Medical School, Dundee Univ, Dundee DD19SY; (2) Cancer Research UK Manchester Inst, The Univ of Manchester, Wilmslow Road, Manchester M20 4BX; (3) School of Psychology and Neuroscience, Univ of St Andrews, St Mary’s College, South St, St Andrews, Fife, KY16 9JP.

NMDA receptor dysfunction is associated with neurological and psychiatric disorders such as Huntington’s disease, schizophrenia, as well as normal aging. Cognitive deficits are a debilitating symptom of these disorders and current treatment is limited. We recently discovered that the major endogenous neurosteroid cerebrosterol has a direct effect on the function of the NMDA receptor. Cerebrosterol increases the function of the NMDA receptor in hippocampal CA1 neurons in culture, and this effect is characterized by an increase in the amplitude of the NMDA-induced EPSP and an increase in the magnitude of the NMDA-induced increase in iCa2+. These effects are observed at concentrations of cerebrosterol that are within the physiological range. The mechanism by which cerebrosterol increases the function of the NMDA receptor is likely to involve a direct interaction with the receptor, as cerebrosterol increases the function of the NMDA receptor in a dose-dependent manner. This finding is consistent with previous studies that have shown that cerebrosterol increases the function of the NMDA receptor in hippocampal neurons. The functional significance of cerebrosterol modulation of the NMDA receptor remains to be determined, but it is possible that cerebrosterol modulates the function of the NMDA receptor in a manner that is relevant to the pathophysiology of neurological and psychiatric disorders.
MA02
NEGATIVE ALLOSTERIC MODULATION OF MGLUR5, BY RO4917523, IMPAIRS TASK PERFORMANCE IN THE 5-CSRTT IN RATS
Isherwood SN. Impulsivity, Boehringer Ingelheim Pharma GmbH & Co. KG, Div. Research, Birkennderfe Strasse 65, Biberach an der Riss, Germany, 88397 sarah.isherwood@boehringer-ingelheim.com
Pecekce A (1), Robbins TW (2), Nicholson JR (1), Dalley JW (2,3) (1) Boehringer Ingelheim Pharma GmbH & Co. KG, Research Germany, Birkennderfe Strasse 65, 88397, Biberach an der Riss, Germany (2) Dept of Psychology, Univ Of Cambridge, Downing St, Cambridge CB2 3EB (3) Dept of Psychiatry, Univ Of Cambridge, Downing St, Cambridge CB2 2QQ

Impulsivity describes a variety of rapidly- and prematurely-expressed behaviours that span several domains from impaired response inhibition to an intolerance of delayed rewards, and is present in attention-deficit hyperactivity disorder, schizophrenia and several forms of addiction. Dysfunctional glutamatergic signalling has consistently been implicated in such disorders; thus targeting the glutamatergic system pharmacologically may be therapeutically useful in modulating impulsive behaviour in humans. In this study, we investigated the role of glutamate in behavioural inhibition in male Lister Hooded rats, weighing 250 - 300 g at the start of the study, by focusing on the role of mGluR5 in modulating premature responding in the five-choice serial reaction time task (5-CSRTT). Following 5-CSRTT training, both non-selected rats and rats exhibiting extreme high (HI) versus low (LI) levels of impulsivity were tested in the 5-CSRTT following pre-treatment with RO4917523, a functionally characterised, negative allosteric mGluR5 modulator. Furthermore, the effect of RO4917523 pre-treatment on impulsivity resulting from NMDA receptor antagonism was investigated using MK801. In a separate group of animals, the effect of RO4917523 on spontaneous locomotor activity was investigated. The main findings indicate that RO4917523 (0.03-1 mg/kg, p.o) dose-dependently decreased premature responding on the 5-CSRTT (main effect p<0.001; dose x vehicle p<0.05, p<0.01 and p<0.01, n=11 per treatment group); an effect that was most pronounced in HI rats at 0.1 mg/kg (group x dose interaction p<0.01, n=12 HI and 12 LI rats). RO4917523 also significantly increased omissions at this dose (p<0.01), suggestive of a non-selective effect on impulsivity at 0.1 mg/kg. However, locomotor activity was unaffected at this dose (p>0.05, n=8 per treatment group). This profile of impairment suggests that RO4917523 may disrupt the attentional or cognitive control over behaviour leading to errors in omission. MK801 robustly increased premature responding in this task (main effect of drug p<0.001, n=8 per treatment group), an effect that was partially blocked by systemic RO4917523 pre-treatment (0.1-0.3 mg/kg). However, since omissions increased in response to RO4917523 treatment, it is unlikely the effects of this compound on impulsivity were selectively mediated. These findings indicate that impulsivity, as measured in the 5-CSRTT, is not selectively modulated by the negative modulation of mGluR5 by RO4917523. However, positive allosteric modulation of mGluR5 may hold promise in the domain of cognitive enhancement. Complete Financial Sponsorship by Boehringer Ingelheim Pharma GmbH & Co. KG, Div. Research Germany, Birkennderfe Strasse 65, 88397, Biberach an der Riss, Germany

MA03
CAPTURING COGNITIVE DEFICITS ASSOCIATED WITH NICOTINE WITHDRAWAL USING A PROBABILISTIC REVERSAL-LEARNING PARADIGM IN RATS
SIlk S. Inst of Neuroscience, Newcastle Univ, The Medical School, Newcastle upon Tyne NE2 4HH s.silk@newcastle.ac.uk
Shoaib M: Inst of Neuroscience, The Medical School, Newcastle Univ, Newcastle upon Tyne, NE2 4HH

The cognitive enhancing effects of tobacco smoking and nicotine have been extensively studied. Nicotine administration has been found to improve cognition; however nicotine deprivation has revealed cognitive impairments and it may be that overall performance is reduced in long-term smokers (Jackson et al; personal communication). This study aims to investigate whether nicotine withdrawal can impair cognitive flexibility. A probabilistic reversal-learning (PRL) paradigm was used to measure cognitive flexibility and assess reward sensitivity, and negative feedback sensitivity. The PRL task presents 2 lights over 199 trials and the correct choice is rewarded by a food pellet on 70% of the trials. All tests consisted of drug administration followed by the PRL task. Nicotine administered acutely (0, 0.025, 0.05, 0.1, 0.2 and 0.4mg/kg SC) to rats (n=8) increased the total time required to complete the task (P=0.042), while varenicline, a nicotinic receptor partial agonist (0, 0.03, 0.1, 0.3 and 1 mg/kg SC) decreased reaction time and total time to complete the task (P=0.001 and P=0.001 respectively). To assess nicotine withdrawal, drug naïve rats (n=16) were randomised into 2 groups and exposed to nicotine (3.16mg/kg/day) or saline chronically via Alzet osmotic minipumps for 7 days. Upon surgical removal of the minipumps, subjects were tested on the PRL task for up to 96 hours. Spontaneous nicotine withdrawal decreased performance across many measures in the PRL task which was time dependent. Performance in the task decreased up to +24 hours shown by a 50% decrease in the number of reversals (P=0.037), increase in average latency to respond (P=0.013) and total time to complete the task (P<0.034). Performance of the rats in the PRL task returned to baseline levels by +72hours, showing recovery from withdrawal. These results provide novel information which could lead to more effective treatments targeting cognition endpoints for diseases such as Alzheimer’s, Parkinson’s and schizophrenia, and presents a better understanding of nicotine withdrawal and dependence. Keywords: nicotine, withdrawal, probabilistic reversal learning, cognition, varenicline. (Financial support from Newcastle University)
Recent work suggests that 5-choice serial reaction time task (5CSRTT) performance can be altered by modulating group II metabotropic glutamate receptors (mGluR2/3) through pharmacology or selective breeding (Wischof and Koch, 2012 Psychopharmacology 219:387-400; Klein et al., 2014 Neuroscience 28:36-45). Using a similar mGluR2 lacking Han Wistar rat from Harlan (UK) to that used previously (Ceolin et al., 2011 J.Neurosci 31:6721-31), we investigated training and baseline performance in the 5CSRTT followed by acute challenges of attention and/or impulse control. Male Charles River control (CR; n=9) and Harlan Han (HSD; n=9) Wistar rats were used for this study. Standard training protocols were used with testing parameters of 5s limited-hold, 1s stimulus duration and 5s ITI. Daily sessions consisted of 30 minutes or 100 trials maximum. Baseline analysis consisted of averaged data from 3 days of testing with a comparison between strains. The acute task challenges used were variable ITI (VITI; 2,4,6,8s), long ITI (LITI; 7s), shortened stimulus (SS; 500ms) and noise distraction (60dB, 500ms). No strain differences over the course of training were observed. Baseline data showed no difference between strains. VITI challenge caused an overall increase in premature% with a significant increase in the CR rats compared to HSD rats (p=0.0175). The SS challenge induced an increase in premature% and a reduction in correct latency in the CR rats compared to HSD rats (p=0.031: 4,p=0.0397), with a trend towards an increase in omissions in the HSD rats (p=0.0765). LITI analysis showed increased premature responding in both strains but no difference between strains was observed. Noise distraction caused a significant increase in omissions (p=0.0076) and correct latencies (p=0.019) in the HSD rats compared to CR rats. No differences in percent correct and collection latency were observed between strains following all challenges. These data show that both Wistar strains train and perform similarly in the 5C-5RTT, unlike selectively-bred Roman rats lacking mGluR2 expression which were more impulsive (Klein et al., 2014). Rats lacking mGluR2 expression are less impaired during tests of increased attentional and impulsive load but more affected by noise distraction. The lack of an impulsive phenotype suggests that mGluR2 loss does not increase impulsivity in this strain. However, the effects of noise may relate to higher anxiety-like behaviours previously reported in a similar Han Wistar strain (Ceolin et al., 2011). ESJR is a senior lecturer at the University of Bristol; CMW is funded by a BBSRC CASE Studentship with Eli Lilly.

Introduction: Although attentional dysfunction is common among neuropsychiatric patients and is linked to quality of life, current treatments remain inadequate. Developing novel treatments requires animal models that recreate the neurobiological aspects of the disease plus measures of treatment efficacy. For the latter, rodent tests having translational validity for human tests are required. The continuous performance test (CPT) is the gold-standard test of attention for psychiatric patients. In humans, the CPT requires activation of the parietal cortex. In contrast, parietal cortical lesions do not affect rodent performance in some attentional tasks, such as the widely used 5-choice serial reaction-time task. Hence, we created the rodent 5-choice (5C-) CPT to provide greater cross-species validity because it also requires the inhibition of responses as do human CPTs. We hypothesized that lesions of the parietal cortex would impair attention in mice tested in the 5C-CPT. Methods: C57BL/6N mice (n=26) were trained in the 5C-CPT. Once stable, mice were subjected to excitotoxic AMPA lesions of the parietal cortices (n=17) or sham lesions (n=9) via 4 burr holes (A-P:-4, L:±3; and A-P:-2, L:±2.25, relative to bregma and the midline, respectively). Once recovered, mice were retrained in the 5C-CPT until sham-lesioned mice attained previous performance levels. Mice were then perfused and lesion location was confirmed using cresyl violet. Results: Upon retraining, both groups exhibited below-chance levels on day 1 and sham mice took 7 days to attain previous performance levels. Across retraining days, mice with parietal cortex lesions performed significantly worse than sham-lesioned mice as measured by d prime (F(1,24)=4.4, p<0.05), with no interaction between days. The parietal lesion did not significantly affect other measures however, including hit rate, false alarm rate, accuracy, or mean correct latency (F$<$1.7, ns). Conclusions: Parietal cortical lesions in mice significantly impaired 5C-CPT performance as measured by d prime, the primary measure of vigilance/attention in human CPTs. This deficit was not only driven by target misses or over-responding to non-targets, but by a deficit in separating responses to targets vs. non-targets. These data are consistent with human CPTs wherein the parietal cortex is activated during target and non-target trials. Hence, this study supports 5C-CPT viability to assess attention in mice as measured in human psychiatric patients. That a human 5C-CPT exists wherein the parietal cortex is activated during target and non-target trials and patients with schizophrenia and bipolar mania exhibit deficient performance further supports the use of this task in cross-species translational studies. These studies were funded by NIH grant support: MH071916 and MH042228, as well as by VISN 22 MIRECC.
**MA06**

**ROLE OF THE PRIMATE ORBITAL AND MEDIAL PREFRONTAL CORTEX IN CONTINGENCY LEARNING**

**Jackson SAW**, Psychology, Univ of Cambridge, Downing St, Cambridge, CB2 3EB sj370@cam.ac.uk

Pears A(2), Horst NK(1,3), Roberts AC(2,3) 1. Dept of Psychology, Univ of Cambridge, Downing St, Cambridge CB2 3EB, UK 2. Dept of Physiology, Development and Neuroscience, Univ of Cambridge, Downing St, Cambridge CB2 3DY, UK 3. Behavioural and Clinical Neuroscience Inst, Downing St, Univ of Cambridge CB2 3EB, UK

Instrumental learning, the ability of an organism to link actions with their outcomes, is crucial for an organism to be able to exploit resources in its environment. The control of instrumental learning can be divided into two components: the stimulus-response/reinforcement ‘habit’ system and a goal-directed mechanism. It has been theorised that a disruption in the balance between these two systems could be responsible for the pathology of obsessive-compulsive disorder (Gillan et al., 2011, Biological Psychiatry, 168(7), 718-26), a neuropsychiatric illness which involves dysfunction in fronto-striatal circuitry. Goal-directed actions have been shown to be dependent upon contingency, defined as the difference between the probability of reinforcement given a response, and the probability of reinforcement in the absence of that response (Hammond, 1980, J Exp Anal Behav, 34, 297-304). The present study therefore utilises a touchscreen-based paradigm (based on that of Balleine and Dickinson, 1998, Neuropharmacology, 37, 407-419) in order to investigate the role of twoprefrontal regions, the medial prefrontal (mPFC) and orbitofrontal cortices (OFC), in contingency learning. The OFC is a region known to show altered activity in OCD patients and the mPFC, having been implicated in rodent contingency learning studies, was chosen for comparison. Marmosets received an excitotoxic lesion of the mPFC (n=4), OFC (n=5) or sham surgery (n=5). Marmosets were then trained on a variable interval schedule whereby responding to a stimulus on the left side of a touchscreen was associated with delivery of reward 1, and responding to a distinct stimulus on the right side was associated with delivery of reward 2, each with a 5% probability of reinforcer delivery given a response. In a subsequent contingency manipulation, one of the reinforcers was presented non-contingently in periods where the subject had not responded, rendering responding to that stimulus causally ineffective. The contingency of response to the other stimulus was unaffected such that responding to the other stimulus could still alter the frequency with which the reinforcer was available. Both the mPFC and OFC lesion groups were insensitive to the contingency manipulation whereas the control group demonstrated selectively increased performance of the non-degraded action as compared to the degraded action. ANOVA comparing the ratio scores of each group revealed a main effect of Group (F(2,11)=5.653; p<0.05) and a Session Pair x Group interaction (F(18,99)=1.733; p<0.05). Subsequent post hoc analysis using the Neuman-Keuls test confirmed the ratio scores of the mPFC and OFC lesion groups were significantly lower than that of the control group for multiple sessions. The mPFC and OFC both play a role in instrumental behaviour via the learning of contingent relationships between actions and outcomes. The neuropsychological implications of this work and its wider relevance within the field of research into the dysregulation of fronto-striatal systems in obsessive-compulsive disorder will be discussed. This study was funded by an MRC Programme Grant (to ACR) and conducted within the University of Cambridge Behavioural and Clinical Neuroscience Institute, supported by a joint award from the MRC and the Wellcome Trust. NH was funded by a Wellcome Trust Programme Grant (PI: TW Robbins). SAWJ was supported by a BCNI-MRC Studentship and AP was supported by an MRC Studentship.

**MA07**

**5-HT DEPLETION PREVENTS THE PROCOGNITIVE EFFECT OF THE DOPAMINE D3 RECEPTOR ANTAGONIST S33084 IN A RAT NOVEL OBJECT DISCRIMINATION TASK**

**King MV**, School of Life Sciences, Univ of Nottingham, Medical School, QMC, Nottingham NG7 2UH madeleine.king@nottingham.ac.uk

Jurkus R, Fone KCF

Visual learning and memory declines with age, is impaired in several psychiatric disorders, and can be assessed in rodents using the novel object discrimination (NOD) task. Although the specific brain regions and neurotransmitters regulating NOD have yet to be fully elucidated, our recent findings indicate performance correlates with prefrontal cortical dopamine release and is enhanced by systemic or local blockade of dopamine D3 receptors in the prefrontal cortex (Watson et al. 2012 Neuropsychopharmacology 37, 770). As 5-hydroxytryptamine (5-HT) stimulates dopamine release in this region (Iyer & Bradberry 1996 J. Pharmacol. Exp. Ther. 227, 40), this study assessed the impact of 5-HT depletion on the ability of a dopamine D3 receptor antagonist, S33084, to delay natural forgetting in the NOD task. 24 male Lister hooded rats (190-240g; CRUK) underwent NOD (Watson et al. 2012) on four occasions at one week intervals to receive saline vehicle (1ml/kg) and S33084 (0.16mg/kg s.c. 30min pre-treatment; Servier, France) on separate test days before and after 5-HT depletion. The tryptophan hydroxylase inhibitor para-chlorophenylalanine methyl ester HCl (pCPA; 150mg/kg; Sigma-Aldrich, UK) or saline vehicle (2ml/kg) were administered i.p. on three consecutive days starting five days prior to the third and fourth NOD tests. At the end of the experiment frontal cortical, hippocampus, striatum and brainstem were collected for quantification of monoamines using HPLC-ED. pCPA caused highly significant decreases in 5-HT and its major metabolite 5-hydroxyindoacetic acid in all regions (P<0.0001 versus control, unpaired t-test with Welch’s correction for unequal variance; 54-93% depletion) without influencing frontal cortical dopamine levels. The NOD choice trial discrimination ratio (time at novel/novel + familiar), with 0.5 being equivalent to chance) did not differ between control and pCPA groups when S33084 were administered before 5-HT depletion, or when vehicle was administered post-depletion. However, when S33084 was administered post-depletion the discrimination ratio was significantly lower in pCPA-treated rats (0.48±0.04) than controls (0.65±0.03; P<0.05, Sidak’s multiple comparison test following repeated measures ANOVA) showing this prevented its pro-cognitive effect. The current findings demonstrate that 5-HT/dopamine interactions contribute to rodent NOD, and future work will use discrete lesions, microinjections and microdialysis to further investigate the underlying neurobiology. Importantly the 5-HT depletion achieved herein was much more extensive than observed in conditions like Alzheimer’s disease, so is unlikely to suggest implications for the potential use of D3 receptor antagonists to treat visual learning and memory in this disorder. Funded by the BBSRC Doctoral Training Partnership programme.
MA08

ASSESSING ATTENTION IN THE MAM E17 RODENT MODEL OF SCHIZOPHRENIA

Malik NN, In Vivo Pharmacology, Eli Lilly & Co., Erl Wood Manor, Windlesham, Surrey, GU20 6PH, malik_nadia@lilly.com
Gastambide F(1), Foss F(1), Lucas E(1), Marston H(1), Gilmour G(1), Tricklebank M(1) (1) Eli Lilly & Co., Erl Wood Manor, Windlesham, Surrey,

Attention deficits are well established symptoms of patients with schizophrenia and are considered valid predictors of impaired cognitive functions. Methylazoxymethanol (MAM) is a neurospecific antimitotic agent that prevents cells from dividing for a short time after injection. Early life exposure to MAM produces persistent behavioural alterations which appear to be akin to core symptoms seen in schizophrenia, including attentional deficits. The aim of this study was to further characterise this rodent model in three different attention assays, the psychomotor vigilance task (PVT), the sustained attention task (SAT) and the continuous performance task (cPT) and to also assess any differences between the routinely used control group where the Dams are injected with saline on embryonic day 17 (hereinafter called SHAM), and an untreated group where the Dams remained un-injected (control). No differences were found between MAM, SHAM and control rats at baseline in the SAT, (p>0.6), and PVT, (p>0.5), tasks. In the cPT task, MAM rats had a normal hit rate (HR), (p>0.2), but were found to have a significantly higher false alarm rate (FAR) than SHAM, (p<0.05), and control rats, (p<0.001). They and also performed significantly more blank touches compared to SHAM, (p<0.001), and control rats, (p<0.001). Task manipulations to make them more difficult or varying effects across the three assays. Increasing the 'wait' ITI in the PVT task from 5s to 10 and 15s had no effect on any PVT performance measure in the MAM rats compared to the SHAMs. Introducing a shorter 25ms stimulus trial in the SAT task or removing correction trials from the cPT task also had no effect in any measure in the MAM treated rats compared to the SHAM or control rats. However, reducing the S+/-S- ratio from 50% to 30% resulted in a lower HR in the control group compared to the SHAM, (p<0.5), and MAM, (p<0.5), treated groups. The increased FAR remained in the MAM treated animals although it was significantly higher compared to the control group, (p<0.001), than to the SHAM group, (p<0.5). The data so far seem to suggest that MAM E17 treated rats have a deficit in impulse control rather than an attentional deficit. Further work will involve the use of distractors and pharmacology to reverse any deficits. This work was funded by Eli Lilly & Company Limited and the IMI NEWMEDS initiative.

MA09

ALZHEIMER’S DISEASE THERAPEUTICS IN A PRE-CLINICAL SPATIAL RECOGNITION PARADIGM: FURTHER EVIDENCE FOR COGNITION-RELATED BELL-SHAPED DOSE RESPONSE CURVES

Godley A, Pre-Clinical Cognition Research, Takeda Cambridge Ltd., 418 Cambridge Science Park, Cambridge, UK CB4 0PA agodley@takedacam.com
Havolli E(1), Hill MDW(1), Goetghebeur PJD(1) (1) 418 Cambridge Science Park, Cambridge, UK, CB4 0PA

Alzheimer’s disease (AD), accounting for approximately two-thirds of all dementia cases, is a relentless and progressive disorder that typically manifests by severe loss of memory (LaFerla FM & Green KN, 2012, Cold Spring Harb Perspect Med, 2:a006320). The aetiology of AD remains largely unknown but impairments in hippocampal function (involved in spatial memory) are among the first symptoms. Pre-clinically, rodents with hippocampal lesions have been shown to be impaired in spatial learning and memory tasks (Puzzo D et al., 2014, Biochem Pharm. 88:450-467). It is clear that continuing efforts to develop disease-modifying drugs are necessary to address AD-associated cognitive decline (Winocur G et al., 2005, Neuropsychologia 43:1580-1590). To this end, it is important for functional effect to take into account the bell-shaped dose response curves commonly reported in various preclinical and clinical cognition paradigms (Schillinga TM et al., 2013, Pyschoneuroendo, 38:1565 – 1572). Data reported here are from a spatial place recognition (SPR) paradigm; a high throughput, hippocampal-mediated memory task (Zhong YM et al., 2000, Physiol. Behav. 69:511-525). The effects of donepezil (acetylcholinesterase inhibitor), memantine (NMDA receptor antagonist) and levetiracetam (nootropic), all of which are used in the clinic to treat cognitive symptoms, were investigated in male C57 mice. The equipment used is a two-chamber spatial recognition apparatus, both chambers differ in shape and pattern. An initial 5 minute ‘sample’ phase allows exploration of one chamber only. Following either a 30 min (remembering) or a 4 hour (forgetting) retention interval, the animal is placed back in the apparatus for a 5 minute ‘choice’ phase, during which it is free to explore both chambers. The exploration time of the novel chamber compared to the familiar was assessed within group by a paired t-test and across groups by a one-way ANOVA followed by Dunnetts post hoc analysis. All compounds tested showed significant pre-cognitive-like effects (P<0.01) with bell-shaped profiles. These results suggest that SPR is a useful tool for assessing rodent hippocampal function and screening potential pre-cognitive compounds. However, as demonstrated by the bell-shaped profiles, it is fundamental that doses are carefully selected to avoid missing a potentially narrow therapeutic window. To conclude: these data back up the growing literature on bell-shaped dose response curves, and further highlight this as an important factor to take into consideration when designing pre-clinical and clinical cognition studies.

MA10

TAU IMMUNOREACTIVITY AND HIPPOCAMPAL SIZE IN A MOUSE MODEL OF HUMAN TAUOPATHY (RTG4510) CORRELATES WITH COGNITIVE PERFORMANCE IN SPATIAL WORKING MEMORY TASKS

Harper AJ, Eli Lilly Co. Ltd, Erlwood Manor, Windlesham, Surrey, KT17 2EZ harper_alex@lilly.com

Mutations in the tau gene in frontotemporal dementia, Alzheimer’s disease and Parkinsonism (FTDP-17) have demonstrated that tau dysfunction can result in neurodegeneration. rTg4510 mice have forebrain restricted expression of a TauP301L mutant protein with high expression in the hippocampus (HPC) and neocortex. From 2.5 months, abnormal biochemical processing of tau and formation of neurofibrillary tangle pathology...
were observed in the neocortex and progressed into the HPC and limbic structures with increasing age. Spatial memory impairment in the Morris water maze has also been observed from 4 months of age, and neurodegeneration and brain atrophy from 6 months. The aim of this study was to extend these findings to another HPC-dependent behavioural task and to determine whether performance could be correlated with pathology. In this study, rewarded and spontaneous alternation, both spatial working memory tasks, were tested in female Tg4510 mice (9 months old, N=20), using a continuous T-maze and a Y-maze. For the T-maze a trial comprised a sample phase, where the animal was forced to turn in one direction, a 5 second inter phase interval and choice phase. The animal was rewarded for alternating arm selection. A session comprised 20 trials or a 1 hour maximum. For the Y-maze, animals were allowed to explore a Y shaped maze for 15 minutes and alternation performance [(3 sequential novel arm entries(N))/(arm entry(N)-2)] was recorded. At the end of the study animals were sacrificed and coronal sections taken and stained for PG5 (pS409) tau immunoreactivity in the dorsal HPC. The hippocampal size was also measured. The data clearly confirmed that the rTg4510 mice had marked hippocampal tau pathology and a 44.3% reduction in hippocampal area. They showed a severe deficit in rewarded and spontaneous alternation performance. Correlation analyses showed alternation performance correlated strongly with tau immunoreactivity (p = 0.02) and hippocampal area (p = 0.005). The correlation between hippocampal area and tau immunoreactivity failed to reach significance (p = 0.08). Data were analysed by ANOVAs followed by planned comparisons as appropriate. Previous data has been published showing a correlation between memory impairment in the Morris water maze and hyperphosphorylated tau levels in the brain. This study confirmed spatial working memory deficits in these mice using rewarded and spontaneous maze tasks. Furthermore, impaired performance in this task was correlated to tangle pathology within the dorsal HPC, and with the hippocampal area. This work was funded by Eli Lilly Co. Ltd.

**MA11**

**THE ROLE OF THE DORSAL HIPPOCAMPUS IN A NOVEL, AUTOMATED OPEN-FIELD SPATIAL NAVIGATION TASK**

**Huxter JR**, Biology, Eli Lilly & Co., Erl Wood Manor Windlesham, Surrey GU20 6PH UK huxter_john@network.lilly.com

Albasser M(1) Gastambide F(1) Hughes R(1) Marston H(1) Dix S(1) (1) Lilly UK, ErL Wood Manor, Windlesham, Surrey GU20 6PH

The human hippocampus is critically important for spatial and episodic memory, and is compromised in numerous conditions such as Alzheimer’s disease and schizophrenia. Consequently, drug discovery programs require efficient preclinical assays for hippocampal function in disease models. Rodent spatial navigation is particularly disrupted by lesions, inactivation, or disruption of the hippocampus, but “gold-standard” rodent hippocampal assays such as the Morris water maze are often labour- and space-intensive, low throughput, or aversive in nature. Based on the “place preference task” originally developed by Jan Bures (Bures et al., 1997) we designed a dry-land alternative to the Morris water maze in which animals must pause in an invisible zone to trigger automatic delivery of a food reward from one of four dispensers at the periphery of an arena (the spatial trigger task). Thirty-two male Lister Hooded rats with dorsal hippocampal lesions and 24 sham-operated controls (280-317g at time of surgery) were trained on daily 30-minute sessions. Occupancy in the trigger zone was measured as a proportion of total occupancy in three additional zones of the same size. Acquisition was compared between the groups and a series of probe trials were used to assess learning strategies. Performance was also assessed on object discrimination and spatial discrimination versions of the task, and on a Y-maze rewarded alternation task. Acquisition of the spatial trigger task did not differ between groups, despite clear deficits in the lesioned rats on rewarded alternation (p<0.01). Both groups performed equally well on unrewarded probe trials in the training arena (chance:25%, sham:59.7%, lesion: 71.3%, n.s.), and were equally disrupted when tested in the arena on the opposite side of the room (1800 rotated orientation). Lesioned animals were only selectively impaired when tested in an un-rotated adjacent arena (sham: 64.0%, lesion: 48.0%, p<0.01), though both groups performed above chance. The results suggest that long acquisition led to overtraining and a resultant bias towards non-hippocampal strategies. Further analysis confirmed that hippocampal animals were more likely to always return to a particular pellet dispenser to aid navigation (p<0.01). Finally, on the rapidly acquired spatial discrimination task, there was an initial lesion deficit but sham levels of performance were achieved by the end of the 30-minute session (p<0.001). We conclude that the spatial trigger task in its current form is unsuitable for assessing hippocampal deficits in disease models, and future variants should include more robust controls for non-hippocampal strategies and be designed to encourage rapid task acquisition to avoid overtraining. All work was funded by Eli Lilly & Co.

**MA12**

**NEW AUTOMATED TOUCHSCREEN LOCATION AND OBJECT-LOCATION TASKS FOR THE MOUSE: EFFECTS OF LESIONS OF THE HIPPOCAMPUS**

**Kim CH**, Psychology, Univ of Cambridge, Downing St, Cambridge, UK, CB2 3EB chk35@cam.ac.uk

Kent BA(1,2), Heath CJ(1,2), Bussey TJ(1,2), Saksida LM(1,2) (1) MRC and Wellcome Trust Behavioural and Clinical Neuroscience Institute, Univ of Cambridge (2) Dept of Psychology, Univ of Cambridge, Downing St, Cambridge CB2 3EB

Tasks such as Trial-unique Delayed Nonmatching-to-Location (TUNL) and Paired-Associates Learning (dPAL) have been developed to test spatial and object learning in automated touchscreen operant chambers. TUNL was originally developed in rats (Talpos et al, 2010, Neurobiology of Learning and Memory, 94, 341-352), but it has not yet been optimised for mice. dPAL has been optimised for use in mice (Bartko et al, 2011, Psychopharmacology, 214, 537-748; Nithianantharajah et al, 2013, Nat. Neuroscience, 16, 16-24), but has yet to be anatomically validated in this species. In this study, we adapted and optimised the TUNL task for use in mice and confirmed the hippocampal dependency of this and the dPAL paradigm with bilateral excitotoxic lesions. In addition, a new version of PAL (context-disambiguated PAL: cdPAL) is described, in which discrimination problems are presented in two separated areas in the touchscreen chamber. For TUNL, 32 male C57BI/6 mice were trained on the task. Based on the final performance level, the mice were assigned to a lesion or a sham group. The lesion group received bilateral dorsal hippocampal injections of NMDA before being tested for post-surgical performance. For dPAL and cdPAL, the subjects were 24 male C57BI/6 mice; half of the mice received NMDA lesions of the hippocampus and half were shams. The number of screen locations used for TUNL was reduced from 14 locations for rats to five locations for mice. dPAL was used without major modification, but for cdPAL a divider was inserted to divide the testing chambers into two spatial
MA13

HIGH FAT / HIGH SUGAR DIET CONSUMPTION DISRUPTS HIPPOCAMPUS-DEPENDENT FEAR MEMORIES

Reichelt AC, School of Psychology, Univ of New South Wales, High Street, Kensington, Sydney, Australia, 2052 a.reichelt@unsw.edu.au
Westbrook RF (1), Maniam J (2), Morris MJ (2) (1) School of Psychology, The University of New South Wales, Sydney, 2052 (2) School of Medical Sciences, The University of New South Wales, Sydney, 2052

The physiological effects of obesity and over-consumption of palatable high fat / high sugar (HFHS) “cafeteria” diets in rats has been shown to induce cognitive deficits in executive function, attention and spatial memory. In this study we utilised a hippocampus mediated non-spatial memory task – trace fear conditioning. The trace interval requires the rats to remember information about the conditioned stimulus (CS), which requires an intact hippocampus. During trace conditioning animals also form associations between the context and the unconditioned stimulus (US - footshock). Therefore we assessed freezing to both the CS (flashing light) and in the context associated with footshock. Adult male Sprague-Dawley rats were fed a diet that supplemented standard lab chow with palatable HFHS foods for 8 weeks, or regular lab chow; the HFHS fed rats rapidly gained weight compared to chow fed controls and were significantly heavier than chow fed controls at test (P<0.001). Overall total levels of freezing did not differ between diet groups, however a dissociation was observed between levels of freezing in the context and to the CS associated with footshock. HFHS diet fed rats froze less than control chow fed rats in the context associated with footshock (P<0.01), indicating that encoding of a hippocampus-dependent context representation may be impaired in these rats. Conversely, HFHS diet fed rats froze more (P<0.05) to the CS than chow fed rats, suggesting that when hippocampal function was compromised the CS was the best predictor of footshock, as contextual information may not be encoded. Postmortem analysis indicated that HFHS diet fed rats had significantly greater white adipose tissue deposits and liver adiposity scores (P<0.001). Hippocampal mRNA expression of inflammatory and neuroplasticity markers were analysed. No change was observed in the inflammatory marker TNF-alpha, however reduced levels of Reelin mRNA, a neuroplasticity-associated protein, was observed, which may contribute to the observed contextual fear memory deficits. Sources of financial sponsorship NHMRC project grant awarded to MJM and RFW; ACR is supported by Australian Research Council Discovery Early Career Research Fellowship.

MA14

A ‘REMINDER’ UNCONDITIONED STIMULUS IS SUFFICIENT TO RECOVER CONTEXTUAL FEAR MEMORY DESPITE THE PRIOR ADMINISTRATION OF ANISOMYCIN INTO THE RAT DORSAL HIPPOCAMPUS

Trent S, Neuroscience & Mental Health, Research Inst, Cardiff Univ, Hadyn Ellis Bldg, Maindy Road, Cathays, Cardiff, Cardiff CF24 4HQ trents@cardiff.ac.uk
Hall J (1), Thomas KL (1) (1) Neuroscience & Mental Health Research Inst, Cardiff Univ, Hadyn Ellis Bldg, Maindy Road, Cathays, Cardiff, CF24 4HQ

Reconsolidation describes the process whereby a fully consolidated memory becomes unstable upon retrieval and must then become restabilised via protein synthesis-dependent processes for the memory to persist. Protein synthesis inhibitors, such as anisomycin, result in a permanent loss of conditioned fear memory (CFM) recall in rodent studies utilising contextual fear conditioning (CFC) and is a key experimental demonstration of reconsolidation. Although anisomycin is thought to block reconsolidation mechanisms, it may facilitate extinction, a process engaged by memory retrieval without the reinforcer. To dissociate between these two alternatives, a low intensity unconditioned stimulus (US) ‘reminder’ cue was exploited in our CFC protocol, following the prior administration of anisomycin into the dorsal hippocampus of rats. The expression of CFM after extinction would be reinstated by exposure of the ‘reminder’ US (which is below the threshold for robust de novo conditioning), whereas the disruption of reconsolidation would result in irrecoverable CFM. Adult, male rats underwent the surgical placement of cannulae, followed by CFC 7 days later (n=6-12/treatment group, 2s foot shock, 0.5mA). Post-US freezing was behaviourally scored (1 minute). 48 hours later, rats underwent recall of the conditioned stimulus (2 minutes) to assess CFM, followed by the immediate bilateral infusion of anisomycin/actinomycin D (80µg/µl and 4ng/µl, respectively) into the dorsal hippocampus (1 µl injected/side, PBS for controls). 48 hours later, the effects of the infusions were assessed in another CS-only exposure (2 minutes) which co-terminated with the reminder US (0.25mA, reminder session) and was immediately followed by a further round of infusions (as above). After 48 hours, rats then underwent a CS-only exposure (2 minutes, LTM1 session) to assess whether the CFM continued to decrease or whether there was stabilisation/recovery of the CFM. As expected, the first anisomycin infusion caused a significant 38 ± 17% reduction in CFM compared with PBS-infused rats (between group effect of TREATMENT: t(8)=3.101, p=0.015 (reminder session); ANOVA with repeated measures interaction of SESSION X TREATMENT: F(1,8)=14.4, P=0.005 (recall v reminder)). Despite a second round of anisomycin infusions, a reminder US was sufficient to reinstate the CFM (no between group of TREATMENT: t(8)=−0.327, P=0.752 (LTM1); ANOVA with repeated measures SESSIONS: F(1,8)=9.521, P=0.015 and an interaction of SESSIONS x TREATMENT: F(1,8)=9.521, P=0.015 (reminder v LTM1)). Therefore, under conditions in which new learning (via consolidation) and memory strengthening (via reconsolidation) are prevented by anisomycin administration into the dorsal hippocampus, CFM is reinstated by a reminder US, suggesting extinction may be facilitated. Work was funded by the Wellcome Trust.
MB01

THE RELATIONSHIP BETWEEN SELF-RATING OF THE EFFECTS OF ALCOHOL (SRE) FORM SCORES AND SUBJECTIVE INTOXICATION AND SLEEPINESS SCORES AFTER ALCOHOL CONSUMPTION

van de Loo AJAE, Div of Pharmacology, Utrecht Univ, Universiteitsweg 99, Utrecht 3584CG The Netherlands a.j.a.e.vandeloo@uu.nl
van Andel N, Verster JC

Introduction: An evening of alcohol consumption often goes at the expense of sleep time. The aim of this study was to determine the relationship between total sleep time and the duration and severity of the alcohol hangover. Methods: A survey was conducted among Dutch university students examining alcohol consumption (amount, start and stop time of drinking), total sleep time and hangover symptoms (presence, severity and duration) during their latest heavy drinking episode. Overall hangover severity (0 to 10 scale) was reported for each two hour period after waking up. Area Under the Curve (AUC) was computed to reflect overall hangover severity. Alcohol consumption and hangover severity were compared for participants who (1) slept less than 5 hours, (2) slept between 5 and 7 hours, or (3) slept more than 7 hours. Results: Data from N=578 students (40.1% men and 59.9% women) were included in the statistical analyses. Their mean (SD) age was 20.0 (2.1) years old and they consume 20.5 (17.3) alcoholic drinks weekly. On average they experience 2.7 (2.4) hangover days per month. On their latest heavy drinking occasions they consumed 8.3 (5.8) alcoholic drinks, followed by 6.6 (2.1) hours of sleep. On average duration of hangover since their last drink was 18.4 (3.9) hours. There was a significant albeit modest correlation between total sleep time and alcohol consumption (r=0.117, p=0.005), hangover severity (r=-0.178, p=0.001) and duration (r=-0.168, p=0.001). In contrast, total alcohol consumption did not correlate significantly with overall hangover severity (p=0.953) and duration (p=0.563). The majority of students (N=313) slept between 5 and 7 hours. Those who slept longer than 7 hours consumed significantly more alcohol (9.3 versus 7.9 and 7.7 drinks, p=0.016), reported extended hangover duration (19.2 versus 18.3 and 17.5 hours, p=0.004), but reported significantly less severe hangovers (20.9 versus 23.9 and 27.5, p=0.001) than students who slept 5-7 or less than 5 hours, respectively. When compared to men, women consumed significantly less alcohol weekly (15.7 versus 27.7 drinks, p=0.001) and on their latest heavy drinking episode (5.8 versus 12.0 drinks, p=0.001) and slept significantly shorter (6.2 versus 6.9 hours, p=0.001). These differences were not reflected in differences between women and men in hangover duration (18.6 versus 18.1 hours, p=0.167) and hangover severity (24.5 versus 22.2, p=0.056). Conclusion: Increased total sleep time is associated with less severe hangovers but has limited impact on the duration. Funding: Utrecht University and Red Bull GmbH.

MB02

TOTAL SLEEP TIME, ALCOHOL CONSUMPTION, AND THE DURATION AND SEVERITY OF ALCOHOL HANGOVER

Verster JC, Div of Pharmacology, Utrecht Univ, Universiteitsweg 99, Utrecht 3584CG The Netherlands j.c.verster@uu.nl
Roth T. Sleep Disorders and Research Center, Henry Ford Health System, Detroit, Michigan, USA

Introduction: An evening of alcohol consumption often goes at the expense of sleep time. The aim of this study was to determine the relationship between total sleep time and the duration and severity of the alcohol hangover. Methods: A survey was conducted among Dutch university students examining alcohol consumption (amount, start and stop time of drinking), total sleep time and hangover symptoms (presence, severity and duration) during their latest heavy drinking episode. Overall hangover severity (0 to 10 scale) was reported for each two hour period after waking up. Area Under the Curve (AUC) was computed to reflect overall hangover severity. Alcohol consumption and hangover severity were compared for participants who (1) slept less than 5 hours, (2) slept between 5 and 7 hours, or (3) slept more than 7 hours. Results: Data from N=46 participants (25 women and 21 men) completed the SRE and their data was used in the analyses. Mean ± SD SRE scores were significantly lower (p=0.001) in women (6.2 ± 2.0) than in men (9.2 ± 2.8). Taking an SRE score > 4.5 as cutoff value, 93.5% (43/46) of participants had a low level of response to alcohol. SRE scores correlated significantly with subjective intoxication at BrAC 0.08% (r = -0.367, p=0.018), but not at lower BrAC levels. SRE scores did not correlate significantly with KSS scores. When controlling for gender and KSS scores at BrAC 0.08%, the correlation between SRE and subjective intoxication was no longer significant (r=-0.235, p=0.150). Conclusion: The association between SRE scores and subjective intoxication at BrAC 0.08% is moderated by other factors such as sleepiness and gender. Funding: Utrecht University and Red Bull GmbH.

MB03

JUST SAY ‘KNOW’: HOW DO CANNABINOID CONCENTRATIONS INFLUENCE USERS’ ESTIMATES OF CANNABIS POTENCY AND THE AMOUNT THEY ROLL IN JOINTS?

Freeman TP, Clinical Psychopharmacology Unit, University College London, Gower St, London, WC1E 6BT tom.freeman@ucl.ac.uk
Morgan CJA(1), Hindocha C(2), Schafer (G), Das RK(2), Curran HV(2) (1)Dept of Psychology, Univ of Exeter, Exeter, EX4 4QG; (2)Clinical Psychopharmacology Unit, UCL, Gower St, London, WC1E 6BT

Introduction: there are over 100 naturally occurring ‘cannabinoids’ which are unique to the cannabis plant, including delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Given the differing pharmacology of THC and CBD and their varied concentrations in cannabis, it is important to understand how people estimate potency and adjust their intake. This study had the following aims: 1) To determine whether measured concentrations of THC and CBD in individuals’ own cannabis predict their estimates of drug potency and actual titration. 2) To ascertain if these effects are influenced by frequency of use and cannabis type. Methods: 247 cannabis users were recruited; the sample consisted of 152 ‘recreational
ASSOCIATIONS OF INTELLECTUAL AND EDUCATIONAL PERFORMANCE WITH ADOLESCENT CANNABIS USE

Mokrysz C, Clinical Psychopharmacology Unit, University College London, London, WC1E 7HB c.mokrysz.12@ucl.ac.uk
Gage S (2), Landy R (3), Munafò MR (4), Roiser JP (5), Curran HV (1) (1) Clinical Psychopharmacology Unit, University College London, UK. (2) School of Social and Community Medicine, Univ of Bristol, UK (3) Centre for Cancer Prevention, Wolfson Inst of Preventive Medicine, London, UK (4) UK Centre for Tobacco and Alcohol Studies and School of Experimental Psychology, Univ of Bristol, UK. (5) Inst of Cognitive Neuroscience, University College London, UK.

Previous research suggests heavy cannabis use in adolescence may lead to persistent neuropsychological deficits. However, the literature is inconsistent, likely because of the difficulty separating the direct effects of cannabis from effects related to confounding variables. A recent longitudinal study suggested chronic heavy cannabis use is associated with a decline in IQ from childhood to adulthood in adolescent-onset cannabis users, but not adult-onset users (Meier et al., 2012). It is important however to investigate other possible explanations for this relationship before drawing a causal conclusion. The present study assessed associations between adolescent cannabis use and intellectual and educational performance, in the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort, attempting to replicate the findings of Meier et al. (2012) in a different, larger sample. Participants completed IQ tests pre-cannabis exposure at age 8 (WISC) and again at age 15 (WASI), and completed cannabis-use questionnaires at age 15. Data linkage with the National Pupil Database provided educational data at Key Stage 2 and 4. A series of nested regression models tested the relationships between cumulative cannabis use and IQ at age 15 and educational attainment at Key Stage 4, controlling for pre-exposure performance and other potential confounders. Of a complete sample size of 2235, 24% reported trying cannabis at least once. Cannabis use was associated with lower IQ at age 15, when controlling for age 8 IQ (p≤.001). Participants reporting using cannabis more than 60 times saw an estimated decline of approximately 3 IQ points relative to never users. Additionally cannabis use was associated with lower Key Stage 4 attainment, when controlling for Key Stage 2 performance (p≤.001). However these associations were dramatically attenuated once other relevant factors (including sex, socioeconomic status, mental health, and other drug use) were statistically controlled for. In particular cigarette, alcohol, and other drug use were strongly associated with decline in IQ and educational attainment. The analyses do not support the findings of Meier et al. (2012), as we see a dramatic attenuation of the association between cannabis use and IQ change once cigarettes, alcohol and other drug use are accounted for. The pattern of attenuation in the series of models suggests that rather than a specific effect of cannabis consumption, any substance use at a young age-and possibly more importantly the risky lifestyle such behaviours reveal, are potentially detrimental to intellectual and academic attainment. Funding: MRC 4-year Studentship.

CAN CO-OCCURRING TOBACCO AND CANNABIS USE PREDICT CANNABIS DEPENDENCE? A FOUR YEAR LONGITUDINAL STUDY

Shaban NDC, Clinical, Educational and Health Psychology, UCL, 1-19 Torrington Place, London, WC1E 7HB natacha.shaban@hotmail.co.uk

A higher frequency of cannabis use is associated with cannabis dependence, yet there are many other factors contributing to cannabis addiction, for example concurrent tobacco use (Peters et al., 2012, Addiction, 107(8), 1404-1417). Little is known about the prospective outcomes of concurrent users. This study aimed to determine the effects of co-occurring cannabis and tobacco use on both current and long-term cannabis dependence. At baseline (T0), 391 regular cannabis and tobacco users self-reported patterns of cannabis and tobacco use (see Morgan et al., 2010, The British Journal of Psychiatry, 197(4), 285-290). They were also assessed for cannabis dependence using the Severity of Dependence Scale (SDS) (range = 0-12; score of ≥3 = dependent). Four years later (T4), semi-structured telephone interviews were conducted with participants (n = 51) that were regular cannabis users at this follow-up time point. Cannabis and tobacco use variables were recorded again, and participants were reassessed on the SDS. Multiple regression analyses at T0 showed that, after controlling for cannabis use, years of tobacco use and days of tobacco use per month were significant predictors of cannabis dependence (M SDS = 2.75, SD = 2.81). Cannabis dependence scores (SDS) increased by 0.17 units for every extra year of tobacco use, and by 0.03 units for every extra day of tobacco use per month (R² = 0.29, p < 0.01). When controlling for the effects of cannabis use and dependence at T0, however, tobacco use at T0 did not predict cannabis dependence at T4. These findings suggest that concurrent tobacco use can predict severity of cannabis dependence at the present time, even after controlling for the independent effects of cannabis use. These results could lead to much needed intervention strategies for dual dependence. This study was supported by the Medical Research Council.
ABSTRACTS

MB06

ABNORMAL HIPPOCAMPAL AND THALAMIC COUPLING OF GLU/CR AND NAA/CR LEVELS IN CANNABIS USERS VS NON-CANNABIS USERS: A PROTON MAGNETIC RESONANCE SPECTROSCOPY STUDY

Kokkinou M, Clinical Sciences Centre, Imperial College London, Hammersmith Hospital, Du Cane Rd, London W12 0NN, UK michelle.kokkinou08@imperial.ac.uk
Mouchlianitis E (1), Bloomfield M (1), Morgan CJ (4, 5), Kokkinou M (1), Curran V (3), Stone J (1), Howes O (1, 2) (1) Psychiatric Imaging Group, MRC Clinical Sciences Centre, Inst of Clinical Sciences, Hammersmith Hospital, Imperial College London (2) King’s College London (3) University College London (4) Clinical Psychopharmacology Unit, Division of Psychology & Language Sciences, University College London (5) Washington Singer Labs, Dept of Psychology, Univ of Exeter

Background: Cannabis is the most widely available and used illicit drug. Few studies investigated the brain metabolite levels in cannabis users and the current literature findings are inconsistent (Sneider et al., 2013, J Addict Res Ther.Suppl 4., pii: 010). We aimed to compare Glu/Cr (glutamate/ creatine) and NAA (N-acetyl-aspartate)/Cr ratios in three brain regions of interest (anterior cingulate cortex, left hippocampus and left thalamus) across subject groups. We also aimed to investigate correlations of Glu/Cr and NAA/Cr metabolite ratios across the three brain regions of interest between subject groups. Methods: We compared Glu/Cr ratio levels and NAA/Cr levels in 16 chronic cannabis users with 16 nonuser subjects. Magnetic resonance spectroscopy on 3T scanner was used and metabolite concentrations were obtained in the three pre-specified voxels using the LCModel. Statistical analyses were performed in IBM SPSS 21. Bonferroni correction was used to correct for multiple comparisons and significance was taken at 0.05 alpha level. Results There were no significant differences in glutamate/Cr and NAA/Cr metabolite ratios in the ACC, the hippocampus or thalamus between cannabis users and non-cannabis users (t(30) = 0.146, p = 0.885 for Glu/Cr and t(30) = 1.38, p = 0.177 for NAA/ Cr in ACC; t(28) = 0.146, p = 0.885 for Glu/Cr and t(28) = -0.704, p = 0.487 for NAA/Cr in hippocampus and t(28) = 0.136, p = 0.893 for Glu/Cr and t(28) = -0.89, p = 0.381 for NAA/Cr in thalamus). In both cannabis and non-cannabis users the Glu/Cr and NAA/Cr were significantly positively correlated in the ACC (r = 0.845, p < 0.05 and r = 0.849, p < 0.05 respectively). In the hippocampus and thalamus Glu/Cr and NAA/Cr levels were significantly positively correlated in cannabis users (r = 0.634, p = 0.011; r = 0.632, p = 0.009, in hippocampus and thalamus respectively) but not in non-cannabis users (r = -0.109, p >0.05, r = -0.11, p>0.05, in hippocampus and thalamus respectively), differences which are statistically significant (z = 2.18, p = 0.03 in thalamus; z = 2.1, p = 0.04 in hippocampus). Conclusion: Cannabis use is not associated with Glu/Cr or NAA/Cr ratios. In healthy controls positive correlations of NAA and Glx (glutamate+glutamine) have been reported previously in the ACC (Waddell et al., 2011, Magn Reson Imaging, 29, 19–24). Here we report abnormal coupling of these metabolites in the hippocampus and thalamus of chronic cannabis users. MRC

MB07

NEUROPSYCHOLOGICAL AND SELF-REPORT DIFFERENCES IN SUBSTANCE DEPENDENT INDIVIDUALS COMPARED TO CONTROLS

Taylor EM, Neuroscience & Psychiatry Unit, Univ of Manchester, Stopford Bldg, Oxford Rd, Manchester, M13 9PT eleanor.taylor-4@postgrad.manchester.ac.uk
Murphy A(1), Ershe KD(2), Flechais R(3), Nutt DJ(3), Lingford-Hughes AR(3), McGonigle J(3), Orban C(3), Passetti F(3), Paterson L(3), Robbins TW(2), Smith DG(2), Deakin J(1), Elliott R(1) (1) Neuroscience & Psychiatry Unit, Univ of Manchester, Manchester M13 9PT, UK (3) Centre for Neuropsychopharmacology, Imperial College London, London W12 0HR, UK (2) Dept of Experimental Psychology, Univ of Cambridge, Cambridge, CB2 3EB, UK

Introduction: Substance dependence is associated with deficits in impulsivity, reward sensitivity and stress reactivity. These deficits are seen in groups dependent on a range of substances but there has been little research comparing groups with different dependencies within a single study. The aim of this study was to investigate cognitive profiles of a large group of substance dependent individuals, to determine whether alterations in impulsivity, reward sensitivity and stress reactivity differ between groups with different dependencies. Methods: Data were collected from 155 participants. Within this cohort, we identified a group dependent on alcohol (n = 28), a group with dependencies on a range of substances, including opiates and stimulants (‘poly-drug’ dependent participants: n = 59), and a group of healthy controls (n = 68). The alcohol and poly-drug dependent groups were abstinent at the time of testing. Participants completed a series of self-report questionnaires associated with addiction, as well as two neuropsychological tasks: the Stop Signal Reaction Time (SSRT) and Intra-Extra Dimensional Set Shift (IED) tasks. Questionnaires included the Beck Depression Inventory (BDI-II), Barratt Impulsiveness Scale (BIS), Behaviour Inhibition/Activation System (BIS/BAS), Childhood Trauma Questionnaire (CTQ), Kirby Delay Discounting Task, Obsessive-Compulsive Inventory (OCI-R), Perceived Stress Scale (PSS-14), Spielbergber State/ Trait Anxiety Inventory (STAI-S, STAI-T), and the UPSIS Impulsive Behaviour Scale (UPPS-P). Results: There was a significant group difference on all questionnaire scores (p < 0.01), except on the BIS/BAS scale. Both alcohol and poly-drug dependent participants had higher scores than controls (p < 0.01) on all the personality traits measured. There were no differences between the substance dependent groups. For the neuropsychological tasks, a group effect was found for the SSRT (p <0.05). Both substance dependent groups were significantly more impulsive than controls, but there was no difference between dependence groups. There were no group differences in the IED. Alcohol dependent participants reported significantly lower childhood trauma than the poly-drug group (p <0.05) on this measure and did not differ from controls. Conclusion: As expected, poly-drug and alcohol dependent groups were significantly different from controls on self-report questionnaires and neuropsychological tasks associated with addiction. However, there were no significant differences between dependent groups on neuropsychological tasks or self-report personality questionnaires. These data suggest that substance dependence is associated with a distinct cognitive profile, but the substance of choice is not relevant. This has implications for optimising approaches to treatment and prevention based on cognitive profiles. Sponsorship: The ICCAM Study is sponsored by the Medical Research Council. ET is a University of Manchester Medical School PhD student, sponsored by the Biotechnology and Biological Sciences Research Council.
MB08

**DOPAMINE FUNCTION IN CIGARETTE SMOKERS: AN [18F]-DOPA PET STUDY**

**Bloomfield MAP, Psychiatric Imaging Group, MRC Clinical Sciences Centre, Mansfield Bldg Hammersmith Hospital, Du Cane Rd London, W12 0NN michael.bloomfield@imperial.ac.uk**

Pepper F(1,2), Egerton A(1,2), Tomasi G(3), Mouchlianitis E(1), Maximen L(4), Veronese M(5), Turkheimer F(5), Selvaraj S(1), Howes OD(1,2)  
(1) Psychiatric Imaging Group, Mansfield Bldg, MRC Clinical Sciences Centre, Inst of Clinical Sciences, Hammersmith Hospital, Imperial College London, Du Cane Rd, London W12 0NN UK (2) Dept of Psychosis Studies, Inst of Psychiatry, King’s College London (King’s Health Partners), De Crespigny Park, London, SE5 8AF UK (3) Comprehensive Cancer Imaging Centre, Imperial Centre for Translational & Experimental Medicine, Hammersmith Hospital, Imperial College London, Du Cane Rd, London W12 0NN UK (4) Hammersmith Imanet Ltd, Cyclotron Bldg, Hammersmith Hospital, Du Cane Rd, London W12 0NN, UK (5) Neuroimaging Dept, Inst of Psychiatry, King’s College London (King’s Health Partners), De Crespigny Park, London, SE5 8AF UK

Introduction: Tobacco addiction is a global public health problem. Addiction to tobacco is thought involve the effects of nicotine on the dopaminergic system. Only one study has previously investigated dopamine synthesis capacity in cigarette smokers. This study, exclusively in male volunteers, reported increased dopamine synthesis capacity in heavy smokers compared to non-smokers. We sought to determine if dopamine synthesis capacity was elevated in a larger sample of cigarette smokers that included females. Methods: Dopamine synthesis capacity was measured in 15 daily moderate smokers with 15 sex- and age-matched control subjects who had never smoked tobacco. Dopamine synthesis capacity (indexed as the influx rate constant Kicer) was measured with positron emission tomography (PET) and 3,4-dihydroxy-6-[18F]-fluoro-l-phenylalanine ([18F]-DOPA). Results: There was no significant group difference in dopamine synthesis capacity between smokers and non-smoker controls in the whole striatum (t28 = 0.64, p = .53) or any of its functional subdivisions. In smokers, there were no significant relationships between the number of cigarettes smoked per day and dopamine synthesis capacity in the whole striatum (r = 0.23, p = 0.41) or any striatal subdivision. Conclusion: These findings indicate that moderate smoking is not associated with altered striatal dopamine synthesis capacity. This study was funded by a Medical Research Council (United Kingdom) grant to Dr. Howes (Grant no. MC-A656-5QD30), a National Institute of Health Research Biomedical Research Council grant to King’s College London. The authors reported no biomedical financial interests or potential conflicts of interest.

MB09

**THE LINK BETWEEN DOPAMINE FUNCTION AND APATHY IN CANNABIS USERS: AN [18F]-DOPA PET IMAGING STUDY**

**Bloomfield MAP, Psychiatric Imaging Group, MRC Clinical Sciences Centre, Mansfield Bldg, Hammersmith Hospital, Du Cane Rd, London, W12 0NN michael.bloomfield@imperial.ac.uk**

Morgan CJA (1,2), Kapur S (3), Curran HV (1), Howes OD (3,4)  
(1) Clinical Psychopharmacology Unit, Div of Psychology & Language Sciences, University College London, 1-19 Torrington Place, London WC1E 7HB (2) Washington Singer Labs, Dept of Psychology, Univ of Exeter, Perry Rd, Exeter EX4 4QG (3) Dept of Psychosis Studies, Inst of Psychiatry, King’s College London (King’s Health Partners), De Crespigny Park, London, SE5 8AF (4) Psychiatric Imaging Group, Mansfield Bldg, MRC Clinical Sciences Centre, Inst of Clinical Sciences, Hammersmith Hospital, Imperial College London, Du Cane Rd, London W12 0NN

Introduction: Cannabis is the most widely used illicit drug in the world and regular use has been associated with reduced motivation i.e. apathy. Regular long-term cannabis use has been associated with reduced dopamine synthesis capacity. The mesolimbic dopaminergic system mediates the processing of incentive stimuli by modifying their motivational value, which in turn is modulated by endocannabinoid signalling. Thus, it has been proposed that dopaminergic dysfunction underlies the apathy associated with chronic cannabis use. Here we examine the relationship between dopaminergic function and subjective apathy in cannabis users. Methods: We measured dopamine synthesis capacity (indexed as the influx rate constant Kicer) via 3,4-dihydroxy-6-[18F]-fluoro-l-phenylalanine ([18F]-DOPA) positron emission tomography (PET) and subjective apathy using the self-rated Apathy Evaluation Scale (AES-S) in 14 regular cannabis users. Results: All subjects scored in excess of 34 points on the AES-S (median [IQR] 59.5[7.5]), indicative of significant apathy based on normative data. Kicer was inversely correlated to AES-S score in the whole striatum (r = -0.23, p = .41) or any striatal subdivision. There were no significant relationships between AES-S and current cannabis consumption (r = 0.28, p = 0.34) or age of first cannabis use (r = 0.25, p = 0.40). Conclusions: These findings indicate that the reduction in striatal dopamine synthesis capacity associated chronic cannabis use may underlie reduced reward sensitivity and amotivation associated with chronic cannabis use. This study was funded by a Medical Research Council (United Kingdom) grant to Dr. Howes (Grant no. MC-A656-5QD30), a National Institute of Health Research Biomedical Research Council grant to King’s College London, and a Medical Research Council (United Kingdom) grant to Professor Curran and Dr. Morgan. The authors reported no biomedical financial interests or potential conflicts of interest.
ABSTRACTS


Wing VC, Schizophrenia Program, Centre for Addiction and Mental Health (CAMH), Toronto, ON, Canada, M5S 2S1 victoria.wing13@imperial.ac.uk

Wing VC1,4, Payer DE2,3, George TP1,3, Boileau I2,3 1 Schizophrenia Div, Complex Mental Illness Program, Campbell Family Mental Health Res Inst, Centre for Addiction and Mental Health, Toronto, ON, Canada; 2 Addiction Imaging Group, Res Imaging Centre (RIC), Campbell Family Mental Health Res Inst, Centre for Addiction and Mental Health, Toronto, ON, Canada; 3 Div of Brain and Therapeutics, Dept of Psychiatry, Univ of Toronto, Toronto, ON, Canada; 4 Imperial College London, London, UK

Positron emission tomography (PET) brain imaging can indirectly measure dopamine (DA) release via DA receptor occupancy. D2/3 receptor tracers have demonstrated that tobacco smoking increases striatal DA release, and these effects correlate with tobacco craving, reward and reinforcement. Nicotine-induced cortical DA release has also been measured in animals but its role in addiction is unclear. The development of high affinity D2/3 radiotracers has facilitated the measurement of cortical DA in humans. We indexed tobacco-induced extrastriatal DA release using the high affinity D2/3 radiotracer [11C]FLB-457 and explored its relationship with addiction-related personality traits such as impulsivity, neuroticism and conscientiousness. Nicotine-dependent daily smokers (n=10) underwent two PET scans after: 1) biochemically verified overnight abstinence and 2) reinstatement of smoking. Voxel-wise [11C]-FLB-457 binding potential (BPND) was estimated in the two conditions and statistical differences between conditions were assessed using paired t-tests (SPM 8). Analyses were restricted to the prefrontal, limbic, and insular regions, with a minimum 50-voxel cluster extent. Correlations between the percentage change in BPND and scores on a Global Assessment of Functioning (GAF), Barratt Impulsivity Scale (BIS) and the NEO Personality Inventory were explored. Smoking was associated with a reduction [11C]FLB-457 BPND compared to abstinence (an indirect measure of DA release) in the cingulate gyrus (voxels=1331: t=5.32, p<0.001), left anterior cingulate cortex / medial frontal gyrus (L ACC/MFG, voxels=148: t=3.45, p=0.004), dorsolateral prefrontal cortex (R/L dlPFC, voxels=323 and 88: t=3.38 and 2.5, p=0.004 and 0.017), amygdala (R/L, voxels=76 and 98: t=3.28 and 3.03, p=0.005 and 0.007), and left insula (voxels=58: t=2.54, p=0.016). The percentage change in BPND in these clusters was 6-14% (SD 7-15%). A greater reduction in BPND (greater DA release) was correlated with increased BIS Attentional Impulsivity (the cingulate gyrus, left amygdala and insula: p's=0.02-0.04), lower openness to experience (cingulate gyrus: p<0.001), and greater neuroticism and reduced openness to experience, conscientiousness and extraversion (insula: p's=0.007-0.07). Lower GAF scores were correlated with a greater BPND reduction in the cingulate gyrus, left DLPFC, right amygdala and left insula (p's=0.003-0.03). Tobacco smoking was associated with DA release in the cingulate gyrus, left ACC and MFG, DLPCF, amygdala and left insula. A greater susceptibility to tobacco-induced DA release in these regions was associated with personality traits typically associated with greater addiction severity such as impulsivity, neuroticism and reduced conscientiousness and overall functioning. As such [11C]FLB-457 may be a useful tool to investigate individual differences in tobacco addiction severity. Internal funds only.

NEURAL RESPONSES TO GAMBLING AND FOOD-RELATED IMAGES IN PATHOLOGICAL GAMBLERS: A FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDY

Limbrick-Oldfield FH, Dept of Psychology, Univ of Cambridge, Downing St, Cambridge, CB2 3EB el371@cam.ac.uk

Mick I(2), Cocks RE(1), Megenigle J(2), Sharman SP(1), Goldstone AP(3), Stokes P(2), Waldman A(4), Bowden-Jones H(4,5), Nutt D(2), Lingford-Hughes A(2), Clark L(1) (1) Dept of Psychology, Univ of Cambridge, Cambridge CB2 3EB, UK (2) Centre for Neuropsychopharmacology, Div of Brain Sciences, Dept of Medicine, Imperial College London, UK (3) Metabolic & Molecular Imaging Group, MRC Clinical Sciences Centre, Imperial College London, UK (4) Faculty of Medicine, Imperial College London, South Kensington Campus, London, SW7 2AZ, UK (5) National Problem Gambling Clinic, Soho Centre for Health & Care, 1 Frith St, London, W1D 3HZ, UK

Introduction: Cue reactivity is a widely used paradigm for studying craving states in addictions research. While pathological gambling is now recognized as a behavioural addiction, cue reactivity has received little attention in this disorder, and past neuroimaging studies have yielded conflicting results, with evidence of both hypo-activity (Potenza et al. 2003 Arch Gen Psychiatry) and hyper-reactivity (e.g. Goudriaan et al 2010 Add Biol). The present study sought to quantify brain responses to gambling-related images, using an appetite (food) control condition. Methods: Functional magnetic resonance imaging (fMRI) was used to assess cue reactivity in a group of pathological gamblers attending the National Problem Gambling Clinic in London (PG, N=13, mean age = 34.5 yrs) and healthy comparison group (HC, N=11, mean age = 33.3 years). Participants viewed blocks of gambling-related images, high caloric food images, and matched neutral images. Results: Craving ratings were taken after each block of images, and indicated a group*cue type interaction, driven by the PG group showing increased urge to gamble after gambling cues, compared to non-gambling cues (F(1,22)=11.60, p<.05). fMRI analysis revealed the PG group showed an increased response in the medial prefrontal cortex and bilateral insula compared to healthy controls (p<.001 uncorrected). Conclusions: Our results complement cue reactivity effects in substance use disorders, showing hyper-reactivity of the medial prefrontal cortex and the insula to gambling-associated cues in treatment-seeking pathological gamblers. This research was funded by the MRC.
MB12

STATE AND TRAIT MARKERS OF IMPULSIVITY AS PREDICTORS OF DISTORTED THINKING IN PATHOLOGICAL GAMBLING

Cocks R, Psychology, Univ of Cambridge, Downing St, Cambridge, CB2 3EB rec61@cam.ac.uk
Sharman S(1), Michalczuk R(1), Bowden-Jones H(2,3), Clark L(1) (1) Dept of Psychology, Univ of Cambridge, Cambridge, CB2 3EB, UK (2) Dept of Medicine, Imperial College, London, UK (3) National Problem Gambling Clinic, Soho Centre for Health & Care, 1 Frith St, London, W1D 3HZ, UK

Background: Pathological gambling is a behavioural addiction associated with a variety of cognitive distortions in the processing of chance and skill. We have previously reported that markers of impulsivity predict higher levels of cognitive distortions in a preliminary sample (n=30) from the National Problem Gambling Clinic in London, U.K. (Michalczuk R, Bowden-Jones H, Verdejo-Garcia A, Clark L (2011). Impulsivity and cognitive distortions in pathological gamblers attending the UK National Problem Gambling Clinic: a preliminary report. Psychological Medicine 41, 2625-2635). The present study aimed to corroborate these observations in an extended sample, further considering distinct facets of impulsivity. Method: Treatment-seeking pathological gamblers (n=90; all male) were compared with male healthy controls (n=45) in a case-control design. Cognitive distortions were measured using the Gambling-Related Cognitions Scale (GRCS). Trait impulsivity was assessed using the UPPS-P impulse behaviour scale, which assesses multiple facets of impulsive behaviour: Urgency, Premeditation, Perseveration, and Sensation seeking. Delay discounting rates were taken as a state measure of impulsive choice. Results: Pathological gamblers showed elevated preference for immediate rewards, compared to controls using a mixed-model ANOVA (F=18.04, p<0.001). The pathological gamblers also displayed elevated impulsivity on UPPS-P urgency, perseveration and premeditation. Effect sizes were largest for urgency (Cohen’s d=1.55). While sensation seeking did not differ significantly between groups, sensation seeking was the strongest predictor of the level of cognitive distortions within the pathological gamblers (r=0.38). Sensation seeking and urgency were independent predictors of cognitive distortions in a multiple regression. Conclusion: Impulsivity is an established marker for a range of addictive behaviours, and pathological gamblers display multiple manifestations of impulsivity, on both state and trait measures. Within the gamblers, higher levels of impulsivity were associated with a greater level of cognitive distortions, with implications for psychological treatments for gambling. Financial Sponsorship: Work was supported by a Medical Research Council (MRC) grant (G0802725; G1100554).

MB13

GABA AND PATHOLOGICAL GAMBLING

Chandrasekera S, Center for Neuropsychopharmacology, Dept Medicine, Imperial College London, c/o Professor Anne Lingford-Hughes, Burlington Danes Bldg, Hammersmith Hospital, Du Cane Rd, London, W12 0NN, sc2910@ic.ac.uk
Mick L (1), Lingford-Hughes A (1) (1) Center for Neuropsychopharmacology, Dept Medicine, Burlington Danes Bldg, Hammersmith Hospital, Du Cane Rd, London

Introduction: Little is known about the roles of GABA in impulsive disorders such as pathological gambling (PG). The relationship between GABA and mechanisms such as impulsivity is of growing interest (Hayes et al 2014; Eur J Neurosci Epub 1-12). We synthesised human literature about GABA and pathological gambling and in related mechanisms such as impulsivity, reward and risky decision-making. Methods: We conducted two searches in MEDLINE, EMBASE and PsycINFO. The first search, ‘GABA and gambling’, used terms relating to GABA/benzodiazepine/baclofen AND gambling, and had to include modification or measurement of any aspect of the GABA system in gamblers or in participants undertaking a gambling task. The second search, ‘GABA and Behavioural Mechanisms’, had to include, in the title or abstract, terms relating to GABA/ benzodiazepine/baclofen AND impulsivity/reward/decision/risk/disinhibition. Due to the large volume of primary studies returned, this search was filtered to only include studies in humans, written in English. Studies had to involve modification or measurement of an aspect of the GABA system and also measurements of gambling behaviour or mechanisms relating to gambling – impulsivity, reward, risk-taking or decision-making. Clinical trials of medications for treatment of addictive disorders, where outcomes did not relate to such mechanisms, and genetic studies were excluded. For both searches, studies had to be accessible online or through the Imperial College London library system. If abstracts met criteria for inclusion, the full text was examined. Results: Together, the searches yielded 1374 studies; 1344 did not meet inclusion criteria and 30 were selected for full review of which 16 met inclusion criteria. One additional study was found through searching cross-references of included studies. Three studies relating to GABA and gambling were included. Two studies measuring CSF GABA reported higher or no difference between PGs and controls. From the studies relating to GABA and behavioural mechanisms, 5 measured GABA levels (4 using MRS, 1 using CSF) and 9 involved modulation of the GABA system with tiagabine, baclofen, or benzodiazepines. GABA levels and impulsivity were reported to be both negatively and positively correlated or not correlated. Baclofen was found to decrease blood flow to brain regions involved in the reward system. Two studies found that benzodiazepines increased selection of risky responses whereas two found no significant correlation. Conclusion: The lack of consistency makes any synthesis challenging. While some studies appear to suggest a role for GABA in pathological gambling and related mechanisms, there is little literature available in humans.
**MB14**


*Mick I*, Centre for Neuropsychopharmacology, Div of Brain Sciences, Imperial College London, UK, Burlington Danes Bldg, Hammersmith Campus, 160 Du Cane Rd, London, W12 0NN i.mick@imperial.ac.uk

Myers J(1), Stokes P(1,2), Colasanti A(2,3), Erritzoe D(1), Searle G(3), Gunn R(3), Waldman A(4), Bowden-Jones H(5), Clark L(6), Rabiner I(3), Lingford-Hughes A(1), Nutt D(1)(1) Centre for Neuropsychopharmacology, Div of Brain Sciences, Imperial College London, UK (2) Inst of Psychiatry, King’s College London, UK (3) Imanova, Centre for Imaging Science, London, UK (4) Dept of Medicine, Imperial College London, UK (5) National Problem Gambling Clinic, CNWL NHS Foundation Trust, Imperial College London, UK (6) Dept of Psychology, Univ of Cambridge, UK

Gambling is a behaviour that around 70% of the British population engage in. In some individuals, gambling spirals out of control and becomes an addiction. Pathological gambling (PG) has an estimated prevalence of 0.5-2% in the UK. The importance of the opioid system in substance dependence is being increasingly recognized. There is strong evidence from recent PET studies that it differs in drug dependent individuals from healthy volunteers’ (HV), in particular higher mu opioid receptor (MOR) levels (Williams et al. (2007). “Brain opioid receptor binding in early abstinence from opioid dependence: positron emission tomography study” Br J Psychiatry 191: 63-9). Consistent with this is that opiate antagonists are effective treatments for addictions, including PG (Potenza (2008). “Review. The neurobiology of pathological gambling and drug addiction: an overview and new findings.” Philos Trans R Soc Lond B Biol Sci 363(1507): 3181-3189). In this study we are testing the hypothesis that PG would be associated with higher MOR levels& blunted endogenous opioid release after an amphetamine challenge compared with HV. We applied our [11C]carfentanil PET imaging with oral amphetamine challenge protocol (Colasanti et al. (2012). “Endogenous opioid release in the human brain reward system induced by acute amphetamine administration.” Biol Psychiatry 72(5): 371-377). 15 male HV (2 smokers, mean age: 34.5), 14 PG (3 smokers, 33.9) underwent two [11C]carfentanil PET scans, one before, one 3hrs after oral administration of 0.5mg/kg of d-amphetamine. Subjective responses to the challenge were measured using the simplified version of the amphetamine interview self-rated scale (SAIRS: euphoria, restlessness, alertness, anxiety). There were no significant differences in baseline availability of MOR. In HV, the amphetamine challenge led to significant reductions in [11C]carfentanil BPND in caudate, putamen, thalamus, cerebellum, frontal lobe, nucleus accumbens, anterior cingulate, insula (all p<0.05). There were no increases in BPND observed. In PG, two regions showed a significant decrease in BPND; Thalamus (0.036), Putamen (0.021). In 5/9 regions BPND increased. Changes in subjective amphetamine ratings were limited. In HV, the mean Δeuphoria scores was +1.2, maxΔ: +3; PG: meanΔ: +1.5, maxΔ: +3. An exploratory analysis of the relationship between Δeuphoria scores and %ΔBPnd did not show significant correlations. Whilst no higher baseline MOR availability was evident, following the amphetamine challenge, blunted endogenous opioid release was seen in PG compared with HV suggesting some opioid dysregulation. Our PET protocol is able to detect changes in [11C]carfentanil binding without participants experiencing an adverse ‘high’. Funding: Medical Research Council- MRC G1002226.

**MB15**

**MU OPIATE RECEPTOR AVAILABILITY IN PATHOLOGICAL GAMBLERS AND RELATIONSHIP WITH IMPULSIVITY: A [11C] CARFENTANIL PET STUDY**

*Ramos AC*, Centre for Neuropsychopharmacology, Div of Brain Science, Faculty of Medicine, Imperial College London, Burlington Danes Bldg, Hammersmith Campus, 160 Du Cane Rd, London, W12 0NN, annacarol.psico@gmail.com

Ramos AC(1)*, Mick I(1)*, Myers J(1), Stokes P(1,2), Erritzoe D(1), Colasanti A(2,3), Bowden-Jones H(4), Clark L(5), Gunn RN(1,3), Rabiner EA(2,3), Searle GE(3), Waldman AD(6), Nutt D(1), Lingford-Hughes AR(1). *These authors contributed equally to this work. (1)Centre for Neuropsychopharmacology, Div of Brain Science, Faculty of Medicine, Imperial College London, UK; (2) Centre for Affective Disorders, Dept of Psychological Medicine, Inst of Psychiatry, King’s College London, UK; (3) Imanova Ltd., Centre for Imaging Sciences, London, UK; (4) National Problem Gambling Clinic, CNWL NHS Foundation Trust, Imperial College London, UK; (5) Lab for Affect, Risk and Gambling Experiments, Dept of Psychology, Univ of Cambridge, UK; (6) Dept of Imaging, Div of Experimental Medicine, Dept of Medicine, Imperial College London, UK

Introduction: Evidence supports a key role for the opioid system in reward. Positron Emission Tomography (PET) studies have shown higher levels of mu opiate receptor (MOR) availability in recently abstinence heroin, alcohol and cocaine addicts and to be related to craving (Lingford-Hughes et al 2010 British Medical Bulletin 96:93-110). Trait impulsivity, a risk factor for some addictions, is also positively correlated with MOR availability (Love et al. 2009. Arch Gen Psychiatry 66(10): 1124-134). No studies have yet quantified MOR availability in pathological gambling (PG), despite evidence for clinical efficacy of opiate antagonists. In this study we used [11C]carfentanil PET to test the hypothesis that MOR availability is higher in pathological gamblers (PG) and is positively correlated with trait impulsivity. Methods: 14 male PG (DSM-IV) and 12 healthy participants (HV) were recruited to the study. Participants had no current or past history of substance dependence (except nicotine) and no neurological or other psychiatric disorders. Impulsivity was measured using the Barratt Impulsiveness Scale (BIS). Participants underwent two [11C]carfentanil PET scans as part of a study replicating Colasanti et al, 2012 (Biol Psychiatry 72(5):371-7). We report here data from the first, baseline scan only. [11C]carfentanil binding potential (BPND) were calculated with a simplified reference region model using the occipital lobe as the reference region for nine regions of interest (ROIs): caudate, putamen, nucleus accumbens, frontal lobe (FL), anterior cingulate (AC), insula, thalamus, amygdala and cerebellum. Results: Total BIS scores ranged from 42 to 88. There was a significant difference in BIS scores between PG and HV participants (p<0.001). [11C]carfentanil BPND did not differ between groups for any ROIs. In the pooled sample, there was no correlation between impulsivity and BPND for any ROIs. Impulsivity was positively correlated with BPND in the caudate only for the HV group [rs = 0.65; p<0.05]. Conclusions: Contrary to our hypothesis, we did not detect an increase in MOR availability in the PG group compared to healthy participants. This difference to previous studies in substance addictions, suggests the possibility that higher MOR is a consequence of drug taking rather than a pre-existing vulnerability marker. However we did find a positive relationship with impulsivity. Financial support: This study was funded by the Medical Research Council- MRCG1002226, GlaxoSmithKline (GSK) and the European College of Neuropsychopharmacology Research Grant for Young Scientists.
**MB16**

**GLOBUS PALLIDUS ABNORMALITIES IN OPIATE DEPENDENCE**
*Tolomeo ST*, Div of Neuroscience, Univ of Dundee, Medical Research Inst, Mail Box 6, Level 6 Ninewells Hospital and Medical School Dundee DD1 9SY s.tolomeo@dundee.ac.uk

Gradin VB(1), Matthews C(2), Gray S(3), Balfour D(1), Johnston B(1), Matthews K(1), Steele JD(1), Baldacchino A(1) (1) CIBPsi, Faculty of Psychology, Univ de la República, Montevideo, Uruguay (2) Div of Neuroscience, Medical Research Inst, Univ of Dundee, Dundee, UK (3) NHS Fife R&D Addiction Services, Scotland, UK

Introduction: Neural and neuropsychological abnormalities occur in diverse human drug addiction populations. However, brain structural and behavioural correlates of patients with opiate dependency have been less studied than some other drugs (Ersche et al. 2013, Curr Opin Neurobiol, 23, 615-624), although there have been occasional radiological reports of gross lesions of the globus pallidus, putatively linked to hypoxic episodes (Kao et al. 2004, Emerg Med Clin North Am, 22, 985–1018; Egan et al. 2005, Nervenartz, 76, 1539–41.). Methods: Brain structure and neuropsychological functioning were investigated for hypothesised abnormalities in forty-seven clinically stable opiate dependent patients with a past history of poly-drug misuse and fifty-one controls. T1 weighted Magnetic Resonance Images were acquired from a representative subset of these volunteers. Results: Patients exhibited significant reductions in the globus pallidus, plus other reductions in the orbito-medial prefrontal cortex, bilateral caudate and putamen. Patients also exhibited significant decision-making abnormalities on the Cambridge Gambling Task (CGT) with regard to risk adjustment, risk taking and impulsivity. The initial titration dose of methadone at the commencement of MMT, which reflected the extent of previous heroin use, and methadone dose at the time of scanning, correlated with grey matter globus pallidus reductions. Abnormal risk adjustment behaviour correlated with reductions in globus pallidus grey matter, increased risk taking with orbitofrontal grey matter reductions, and increased impulsivity with cingulate cortex reductions. Conclusions: These findings support an interpretation of heightened risk taking and impulsivity in patients with opiate dependency. The anatomically restricted correlates of indices of methadone exposure to the globus pallidus may be linked to a risk of hypoxic events. Orbitofrontal and cingulate reductions may be linked to poly-substance misuse prior to clinical stabilisation on methadone. Financial sponsorship: This study was part funded by an unrestricted educational grant provided by Schering-Plough and a grant by an Anonymous Trust.

**MB17**

**BRAIN STRUCTURAL ABNORMALITIES AND MOOD SYMPTOMS IN OPIATE-DEPENDENT PATIENTS RECEIVING METHADONE MAINTENANCE THERAPY**
*Tolomeo ST*, Div of Neuroscience, Univ of Dundee, Div of Neuroscience, Medical Research Inst, Mail Box 6, Level 6 Ninewells Hospital and Medical School Dundee, DD1 9SY s.tolomeo@dundee.ac.uk

Baldacchino A(1), Matthews K(1), Steele JD(1) (1) Div of Neuroscience, Medical Research Inst, Univ of Dundee, Dundee, UK

Introduction: Several brain circuits are relevant in the neurobiology of addiction (Koob et al. 2010, Neuropsychopharmacology, 35, 217-381). Here we highlight symptoms related to mood, anhedonia and anxiety associated with drug misuse. These symptoms might represent a risk factor for addiction. Brain regions linked to stress reactivity, drug craving and mood participate in addiction but their involvement has been much less investigated in the human brain (Volkow et al. 2011, Proceedings of the National Academy of Sciences, 108, 15037-15042). Methods: We acquired T1 weighted structural brain images from 30 patients on methadone maintenance therapy. Mood, anhedonia and anxiety symptoms were measured using the BDI, Snaith Hamilton and HAD-Anxiety. We tested the hypothesis of no relationship between mood, anhedonia and anxiety ratings and brain structure. Results: Patients exhibited significant correlations with BDI, Snaith Hamilton, HAD-Anxiety. In particular, higher BDI scores correlated negatively with grey matter probability in the bilateral hippocampus, amygdala and insula. HAD-Anxiety scores correlated negatively with the bed nucleus of stria terminalis and medial temporal lobe. Snaith Hamilton scores correlated negatively with nucleus caudate and ventral tegmental area. In mood disorder without drug dependency, similar correlations have been reported (Bora et al. 2012, Journal of affective disorders, 138, 9-18). Conclusions: As drugs can subjectively reduce anxiety and anhedonia during intoxication, but with potentially enhanced symptoms during withdrawal, this suggests that repeated use of such drugs may be used to self-treat such symptoms. The problem with such repeated self-treatment is long-term worsening of the symptoms due to allostatic adaptation (Koob et al. 2001, Neuropsychopharmacology, 24, 97-129). If so, this may reflect a maintaining factor for regular drug misuse. Financial sponsorship: This study was part funded by an unrestricted educational grant provided by Schering-Plough and a grant by an Anonymous Trust.

**MB18**

**WHEN IS ENOUGH ENOUGH? REDUCED RELIANCE ON PERCEPTUAL EVIDENCE IN OCD**
*Banca P*, Psychiatry, Univ of Cambridge, Addenbrooke’s Hosp, Cambridge CB2 2QQ paula.banca@gmail.com

Vestergaard MD(1), Rankov V(2), Mitchell S(2), Lapis T(2), Irvine M(2), CasteloBranco M(3) and Voon V(2) (1) Dept of Physiology, Development and Neuroscience, Univ of Cambridge, Cambridge CB2 3DY (2) Dept of Psychiatry, Univ Of Cambridge, Addenbrooke’s Hosp, Cambridge CB2 2QQ (3) Inst for Biomedical Imaging and Life Sciences, Univ of Coimbra, 3000-548 Coimbra, Portugal

Introduction: Compulsive behavior may be conceptualized as excessive gathering of evidence before commit to a decision possibly to reduce uncertainty. Here we investigate the process of evidence accumulation in Obsessive Compulsive Disorder (OCD) in perceptual discrimination and probabilistic reasoning, hypothesizing impairments in both decision types. Methods: Twenty-eight OCD patients and 35 healthy control subjects were tested with a low-level visual perceptual task (random dot motion task), a probabilistic reasoning task (jumping to conclusions task) and two
response conflict tasks as control tasks (Flanker task and reinforcement learning conflict task). Logistic regression analysis across all coherence levels (which accounted for visual detection threshold) and hierarchical drift diffusion modeling (HDDM) were used to characterize response strategies between patients with OCD and healthy controls in the random dot motion task. Results: In both the behavioural and computational approaches, OCD patients compared to healthy volunteers were more cautious in weighing the alternatives and accumulated more evidence (longer reaction time, response time intercept and higher choice boundary) particularly to high uncertainty in the visual perceptual but not probabilistic reasoning task. This behaviour was more evident in patients with higher compulsivity scores. The HDDM analysis showed higher choice boundaries, or evidence needed to make a decision in high uncertainty and slower drift rate reflecting poorer quality of evidence in low uncertainty in OCD subjects (for explanation of these constructs, see Ratcliff and McKoon, 2008, Neural computation, 20, 873-922). With a penalty cost for speed, OCD subjects reversed the difference in decision boundaries, accumulating less evidence, in low uncertainty trials compared to healthy volunteers, without compromising accuracy. These findings were unrelated to high-level visual perceptual deficits and response conflict. Conclusions: We highlight the convergence and divergence of behavioural and computational approaches to evidence accumulation in OCD demonstrating a differential influence of high and low uncertainty contexts on evidence accumulation and on the quality of evidence. We further emphasize that OCD subjects are sensitive to an external salient penalty cost on evidence accumulation without compromising accuracy, possibly by influencing internal cost-benefit ratios. These findings may have relevance for therapeutic approaches. This work was supported by the Wellcome trust and the Portuguese Foundation for Science and Technology.

MB19

ACUTE EFFECTS OF ALCOHOL ON THE RESTING BRAIN: A MAGNETOEENCEPHALOGRAPHY STUDY

Campbell A, CUBRIC, School of Psychology, Cardiff Univ, 70 Park Place, Cardiff, CF10 3AT campbellae1@cardiff.ac.uk
Sumner P(1), Singh KD(1), Muthukumaraswamy SD(1) (1) CUBRIC, School of Psychology, Cardiff Univ, 70 Park Place, Cardiff, CF10 3AT

Alcohol is a rich drug affecting many neurotransmitter systems, but in particular the GABAergic and glutamatergic systems. This disruption to the balance between excitation and inhibition can affect the brain oscillations as measured by magnetoencephalography (MEG). Previous research studying the brain at rest has determined that acute alcohol administration decreases beta power and increases alpha power during an eyes-closed paradigm with analyses in both sensor space and source space. fMRI of the resting brain has been used to investigate network connectivity. Alcohol increases BOLD amplitude specifically within the visual network. Nevertheless, it is argued that MEG is better suited to the study of the brain at rest due to its independence from neurovascular confounds. In this single-blind, placebo-controlled crossover study, 15 healthy participants (mean age 25.9 years SD 3.8, 8 female) completed two study days, one in which they consumed a dose of 0.8g/kg alcohol, and the other a placebo. MEG recordings of wakeful resting brain activity in an eyes-open paradigm were taken before and after beverage consumption. Five minutes of resting data were recorded during each session. Peak breath alcohol (BrAC) reached a mean of 36.4 µg/100ml (SD = 6.2 µg/100ml). Within-subjects 2x2 ANOVAs revealed there was a significant slowing of saccadic eye movement velocity under alcohol intoxication (p<.05) indicating sufficient sedation. Subjective ratings of drunkenness were also significantly higher following alcohol compared to placebo (p<.05). Cluster randomisation analysis of sensor-space MEG data were used to compute differences between pre- and post-drink scans. T-tests on these differences revealed a significant power increase in alpha (8-13Hz, p<.01), beta (13-30Hz, p<.01) and low gamma (30-50Hz, p<.05) frequency bands. These significant increases were observed over central parietal areas. Acute effects of alcohol on resting state network connectivity were also investigated. These findings confirm those of previous research but also indicate the presence of a significant influence of alcohol on the resting brain in an eyes-open paradigm. Increases in both beta and gamma power have not previously been reported at this dose or sample size. A Campbell receives a PhD studentship from Alcohol Research UK and the research was supported by the MRC MEG UK Partnership grant.

MB20

ICCAM PLATFORM STUDY: AN INVESTIGATION INTO THE EFFECTS OF THE D3 ANTAGONIST GSK598809 ON ANTICIPATION OF REWARDS IN ABSTINENT ALCOHOL AND POLY-DRUG DEPENDENT INDIVIDUALS

Murphy A, NPU, Univ of Manchester, G.708 Stopford Bldg, Oxford Rd, Manchester, M13 9PT anna.murphy@manchester.ac.uk
McGonigle J (2), Ersche KD (3), Flechais R (1), Lingford-Hughes A (2), Nestor L (4), Nutt D (2), Orban C (2), Robbins T (3) Smith D (3), Suckling J (3), Elliott R (1), Deakin JW (1), (1) Neuroscience and Psychiatry Unit (NPU), Stopford Bldg, Univ of Manchester, Manchester, M13 9PT (2) Centre for Neuropsychopharmacology, Div of Brain Sciences, Imperial College London, Hammersmith campus, London W12 0NN (3) Behavioural and Clinical Neuroscience Inst (BCNI), Univ of Cambridge, Cambridge (4) GlaxoSmithKline Clinical Unit, Addenbrooke’s Hospital, Cambridge, CB2 0GG

The high rate of relapse to drug and alcohol use following initial successful treatment is a core problem facing the treatment of addiction. Dysregulation of neurobiological networks are thought to underlie increased vulnerability to relapse. The ICCAM study aims to target these networks with pharmacological agents with strong theoretical links to relapse vulnerability. One such vulnerability network is the reward system - evidence from neuroimaging studies suggest a biasing of reward system activation towards drug-related stimuli, at the expense of non-drug reward stimuli in addiction. These lines of evidence suggest two possible approaches in the treatment of reducing relapse vulnerability; reducing brain responses to drug or alcohol reward cues, and enhancing blunted reward functioning to non-drug reward cues. GSK598809 is a dopamine D3 preferring receptor antagonist that has shown promise in preclinical models of drug relapse. D3 receptors are preferentially expressed within the limbic reward system including the ventral striatum and midbrain (Searle et al. 2010, Biol Psychiatry), and are therefore ideally located to modulate reward system functioning. Although the exact function of D3 receptors within the midbrain is yet to be determined, its location is suggestive of an antireceptive function. We aimed to investigate the effects of GSK598809 on brain response to non-drug reward stimuli using the monetary incentive delay task (MID) (Knutson et al. 2000, Neuroimage) Alcohol dependent (AD), poly-drug dependent (PD), and healthy control (HC) participants.
received 60mg GSK598809 or placebo following a double blind procedure 2 hours before fMRI scanning with the MID task. The MID task comprised of win, loss, and neutral trials (event-related). Data were acquired with 3 Tesla scanners (Philips Achieva and Siemens Trio). Data from 18 ADs, 23 PDs and 23 HCs were analysed using FSL (Z > 2.3, corrected cluster significance threshold of p < 0.05). GSK598809 did not produce any significant behavioural effects. In the AD group, GSK598809 increased BOLD response during anticipation of winning compared to placebo within the caudate and globus pallidus. In the PDs, GSK598809 enhanced BOLD response to the anticipation of winning within the putamen compared to placebo. No effects of GSK598809 were found in the HCs. GSK598809 enhanced striatal responsiveness to non-drug rewards in dependent participants. Such effects may be due to antagonism of D3 receptors within the midbrain to enhance striatal dopamine release. These findings suggest GSK598809 may reduce relapse vulnerability by restoring deficient reward responsivity in dependent individuals. The ICCAM Study is funded by the Medical Research Council (MRC)

MB21
ICCAM PLATFORM STUDY: THE ANTERIOR CINGULATE AND MEDIAL FRONTAL CORTEX TRACK MONETARY REWARDING OUTCOMES IN ABSTINENT ALCOHOLICS ON NALTREXONE

Nestor LJ, Behavioural and Clinical Neuroscience Inst, Univ of Cambridge, Addenbrooke’s Hospital for Clinical Investigation, Cambridge, CB2 0GG

Murphy A (1), McGonigle J (2), Orban C (2), Taylor E (1), Flechais R (2), Paterson L (2), Smith D (3), Ersche KD (3), Suckling J (3), Tait R (3), Elliott R (1), Deakin B (1), Robbins TW (3), Lingford-Hughes A (2), Nutt DJ (2) (1) Neuroscience and Psychiatry Unit (NPU), Stopford Bldg, Univ of Manchester, Oxford Rd, M13 9PT (2) Centre for Neuropsychopharmacology, Div of Brain Sciences, Dept of Medicine, Imperial College London, Hammersmith Campus, 160 Du Cane Rd, London W12 0NN (3) Behavioural and Clinical Neuroscience Inst, Univ of Cambridge, Cambridge, CB2 3EB

Introduction: There is strong evidence supporting an association between the endogenous opioid system and the rewarding effects of alcohol. Alcohol produces its effects through mu opioid receptor (MOR) disinhibition of midbrain dopamine neurons. Alcoholics have an increased number of MORs within frontostriatal regions during early abstinence, with suggestions that there may be a reorganization (or “hijacking”) of reward circuitry priorities in alcohol dependence - there is a blunted response to non-alcohol rewards akin to a reward deficiency syndrome. Naltrexone is a MOR antagonist currently licensed for alcohol dependence, and which may have a modulating effect on MOR-driven alterations within frontostriatal reward circuitry. Therefore, we examined the acute effects of naltrexone in early abstinent alcoholics in an attempt to elucidate the effects of MOR blockade on the neural correlates of non-alcohol reward processing. Methods: Alcohol dependent (AD: N=22; 4 females; mean age = 45.3 years) and healthy control (HC: N=36; 8 females; mean age = 41.1 years) volunteers completed a monetary incentive delay task on two separate, randomized study visits: once after receiving 50mg of the naltrexone, and once after receiving placebo. We took an a priori approach to our analyses, restricting our search for group differences within a collection of frontostriatal regions (i.e. caudate, putamen, nucleus accumbens, insula, medial, orbital and anterior cingulate cortex). Significant clusters were determined by thresholding at t>2.3 with a corrected (FWE) cluster significance threshold of p<0.05. Results: No behavioural group differences were observed. In response to monetary reward gains, the AD group showed significantly less activation in the rostral anterior cingulate cortex (rACC) while on placebo compared to the HC group. On naltrexone the AD group showed significantly more activation in the ACC and medial frontal cortex (MFC), but reduced activation in the orbitofrontal cortex (OFC), compared to the HC group. Following monetary reward misses, the AD group demonstrated an increased activation in the bilateral caudate, but a reduced activation in the bilateral insula compared to the HC group while on naltrexone. Conclusions: Reduced activation in the “affective” rACC of the AD group on placebo suggests some reward deficiency that resolves under naltrexone. Enhanced ACC and MFC activation, with reduced OFC activation, may indicate a reorganization of implicit motivational value and incentive salience in frontostriatal regions, following naltrexone. Increased caudate activation in response to monetary reward misses suggests that naltrexone modulates negative prediction error signalling at the expense of translating interoceptive states into insula-driven emotional responses in alcoholics. Funding Medical Research Council (MRC G1000018)

MB22
THE MODULATORY EFFECTS OF NALTREXONE ON THE UNDERLYING NEURAL NETWORK IN ALCOHOL AND DRUG DEPENDENCE: AN FMRI STUDY

Savulich G, Psychiatry, Univ of Cambridge, Herchel Smith Bldg for Brain and Mind Sciences, Forvie Site, Robinson Way, Cambridge CB2 0SZ

gjs46@medschl.cam.ac.uk


Introduction: The processing of emotional information is associated with altered functional response in the limbic system in addiction. For example, increased activation of visual emotional processes such as the insular cortex and fusiform gyrus in response to negative pictures and, conversely, decreased activation of the dorsal and ventral striatum in response to positive pictures has been shown in individuals with substance dependence. Naltrexone is one pharmacotherapy used in the management of opioid and alcohol dependence. It has been suggested that naltrexone works by modulating activation of the mesolimbic pathway, one network associated with emotion-related behaviour. We hypothesized that alcohol and drug-dependent individuals would demonstrate increased neural response to highly threatening pictures on placebo compared to healthy matched control
volunteers and that a single dose of naltrexone would modulate this activation in the two substance-dependent groups. Method: This study was a multicenter, placebo-controlled, single-dose, double-blind crossover design. 74 participants (n=22 abstinence alcohol-dependent, n=24 abstinence drug-dependent [alcohol plus at least one other drug dependence] and n=28 healthy volunteers) were administered either placebo or 50 mg naltrexone. During fMRI scanning, participants were instructed to attend to a series of pictures. Highly aversive pictures (e.g. injuries, accidents) were compared to neutral pictures (e.g. landscapes, household objects) selected from the International Affective Picture System. Images were balanced for valence ratings and presented in a block design in two runs of four blocks each, with each block containing six images. Each block was separated by a rest period to prevent habituation effects. Significant between-group differences were identified at the whole-brain level with appropriate family wise error correction for multiple comparisons. Results: Processing of threatening pictures in relation to neutral pictures on placebo revealed increased activation in frontostriatal clusters including the orbitofrontal cortex, anterior cingulate gyrus, caudate nucleus and putamen regions in the alcohol and drug-dependent individuals and decreased activation in these regions in healthy volunteers. Although naltrexone decreased (i.e. ‘normalised’) activation within this frontostriatal network in both alcohol and drug-dependent individuals, the modulation by naltrexone was significantly greater in the drug-dependent group compared to the alcohol-dependent and healthy volunteer groups. Conclusions: Function of one neural network underlying emotional processing is heightened in alcohol and drug dependency. Over-activation in the frontostriatal network during emotional processing of threatening pictures in abstinent alcohol and drug-dependent individuals was differentially modulated by a single dose of naltrexone. Clinical implications of these findings warrant further investigation. The ICCAM platform study is funded by the Medical Research Council (MRC) of the United Kingdom.

MB23

RESISTING THE URGE TO SMOKE: EFFECTS OF INHIBITORY CONTROL TRAINING IN CIGARETTE SMokers
Adams S, Dept of Psychology, Univ of Bath, 2 South Claverton Down, Bath, BA2 7AY s.adams@bristol.ac.uk
Mokrysz C (2), Attwood AS (3,4), Munafò MR (3,4) (2) Univ Coll London, UK; (3) UK Centre for Tobacco and Alcohol Studies and School of Experimental Psychology, Univ of Bristol, UK; (4) MRC Integrative Epidemiology Unit (IEU) at the Univ of Bristol, UK

Smokers have difficulty in resisting smoking urges. Research has explored the possibility of using inhibitory control training (ICT) to improve response inhibition, in order to reduce alcohol intake (Houben, et al. (2011). “Resisting temptation: Decreasing alcohol-related affect and drinking behavior by training response inhibition.” Drug and Alcohol Dependence 116(1-3): 132-36). However, there has been no research on ICT in cigarette smokers. This study assessed the effects of ICT on inhibition and cigarette use in smokers. We hypothesised that ICT would improve response inhibition, and reduce cigarette use. 55 current smokers (52% male; aged 18-50) abstained from smoking for 12 hours prior to the test day. On the test day, participants recorded cigarette use for the past 7 days and completed pre-training measures of global and cue-specific (i.e., smoking-related) response inhibition, using a go/no-go task. Participants were randomised to an ICT group (active, control). The active training group was required to repeatedly inhibit a response towards smoking cues (100%), while the control group was required to inhibit a response towards smoking and neutral cues with equal frequency (50%). Participants performed post-training measures of response inhibition, a resistance to smoking task, and recorded cigarette use for the next 7 days. Primary outcomes were assessed using ANOVAs of commission errors (failures to inhibit), with a within-subjects factor of time (pre-/post-training) and a between-subjects factor of training group (active/control). The cue-specific version included an additional factor of cue (smoking/neural). Our secondary outcome of smoking resistance was assessed using logistic regression, while cigarette use was examined by ANOVA of number of cigarettes per week, with a within-subjects factor of time and a between-subjects factor of training group. Error data did not indicate the hypothesised time × group or time × group × cue interactions. Smoking resistance data indicated that, as hypothesised, smokers in the active group were more likely to be able to resist smoking for a period of 20 minutes than those in the control group (OR = 2.65, 95% CI 0.84 to 8.34, p = 0.095). Cigarette use data did not indicate the hypothesised time × group interaction. Our data suggest that ICT enhances the ability to resist smoking, indicating that training may be a promising adjunct to smoking pharmacotherapy. Further research is required to improve the duration of training effects and to understand the mechanism underlying training. Funding: University of Bristol, School of Experimental Psychology Pilot Grant

MB24

THE EFFECTS OF NICOTINE DEPENDENCE AND ABSTINENCE ON THE PROCESSING OF DRUG AND NON-DRUG REWARDS IN CIGARETTE SMOKERS
Lawn W, Clinical Psychopharmacology Unit, Clinical Educational and Health Psychology Dept, University College London, Gover St, London, WC1E 6BT will.lawn.12@ucl.ac.uk
Freeman TP(1), Hindoacha C(1), Mokrysz C(1), Das R(1), Morgan CJA(2), Curran HV(1) (1) Clinical Psychopharmacology Unit, Clinical Educational and Health Psychology Dept, UCL, Gower St, London, WC1E 6BT; (2) Psychology Dept, Univ of Exeter, Exeter, Devon EX4

It has been proposed that drug addiction is characterised by an overvaluation of drug rewards and an undervaluation of non-drug rewards. This imbalance in reward processing may become further disordered during states of acute abstinence. The differences in reward processing of cigarette and non-drug rewards between dependent smokers and occasional smokers and the effect of acute nicotine abstinence on this remains unclear. To determine the differences in choices for, motivation for and liking of cigarette and non-drug rewards between dependent and occasional smokers and test the effect of 12 hour nicotine abstinence. Dependent (n=20) and occasional smokers (n=20) were tested after ad libitum smoking and at least 12 hours of nicotine abstinence. A novel task, the DReaM-Choice, was developed in which participants could win different rewards: cigarettes, music, chocolate and paper (a neutral outcome). Participants were given a series of two-option choices between different rewards and could then work for the chosen reward by pressing a button quickly. Number of choices and average number of button-presses associated with each reward were recorded. Subsequently, participants ‘consumed’ the rewards they accrued and rated their subjective liking to each ‘unit’ of each reward. Self-
reported wanting, anhedonia, withdrawal symptoms and affect were also assessed. Dependent smokers made more choices for, pressed more for, reported more wanting of and more liking of a cigarette reward compared with occasional smokers. Moreover, dependent smokers made fewer choices for chocolate and music compared with occasional smokers. Dependent smokers and occasional smokers also exhibited different profiles in terms of their choices, button-pressing, wanting and liking: dependent smokers, in general, had similar processing of cigarettes, chocolate and music, while occasional smokers, in general, had increased processing for one or both of the non-drug rewards compared with cigarettes. 12 hour nicotine abstinence led to more cigarette choices and fewer music choices, when collapsed across groups. An exploratory finding, although just a trend, was that dependent smokers chose fewer large rewards and more small rewards than occasional smokers. Dependent smokers appeared to overvalue cigarette rewards relative to occasional smokers on a variety of reward-processing indices. There was little evidence of undervaluation of non-drug rewards in dependent smokers relative to occasional smokers. Surprisingly, nicotine abstinence did not have a differential effect on dependent and occasional smokers, but did increase choices for cigarettes and decrease choices for music in both groups. There was also some evidence to suggest that dependent smokers were less sensitive to reward magnitude overall. This study supports the notion that nicotine dependence is associated with an overvaluation of cigarette rewards but the position of non-drug rewards remains unclear. Furthermore, this study casts doubt upon the specific effect of nicotine abstinence on reward processing in dependent smokers relative to occasional smokers. BBSRC funds WL’s PhD

MB25

AVERSION REVISITED: LEVERAGING RECONSOLIDATION TO UPDATE THE MOTIVATIONAL STATUS OF ALCOHOL CUES

Das RK, Clinical Psychopharmacology Unit, UCL, 1-19 Torrington Place, London WC1E 7HB ravi.k.das@gmail.com.
Lawn W (1), Kamboj SK (1)

Introduction: Updating cue-drug associations via memory reconsolidation may offer a viable new long-term approach to targeting the maladaptive associative memories that underpin relapse susceptibility in alcohol use disorders. Here we investigate the efficacy of a novel methodology using prediction error at recall to destabilise cue-drug memories in heavy drinkers and update these associations with disgust-based counterconditioning.

Method: Hazardous beer drinkers’ memories of prototypical cue-drinking associations were first reactivated with a reward prediction error (REACT + PE) or without (REACT no PE) or were not recalled (Control). Ten minutes after this, beer cues (CS+) were paired with either disgusting images or tastes (0.06% Bitrex solution). Soft drink images (CS-) were paired with neutral pictures. CS liking ratings and eye movements were recorded throughout the task. Seven days later, participants’ liking of the CSs, cue-induced craving and attentional bias to the CSs and novel alcohol cues was assessed. Timeline follow-back assessed changes in drinking across the study. Results: The REACT + PE group showed lower liking of alcohol CSs and novel alcohol cues relative to neutral CSs at test. This was not seen in the REACT no PE and Control groups [Stimulus Type x Group interaction F(6, 165) = 2.407, p = 0.029, η2p = .08]. Correspondingly, the REACT + PE GROUP showed an abolition of attentional bias to alcohol CSs at test [Stimulus Type x Group interaction F(6, 162) = 3.293, p = 0.01, η2p = .16]. Reductions in beer drinking were predicted by cue evaluation in The REACT + PE group only [r(20) = .623, p = 0.003] and this group showed reduced positive expectancy of alcohol compared to Control [t(36) = 2.8, p = 0.008, r = 0.42]. Discussion: This is the first demonstration of reconsolidation-update mechanisms reducing explicit liking, motivational salience and outcome expectancy of alcohol cues one week later. Effects were prediction-error dependent, as similar effects were not seen with counterconditioning alone or without PE at recall. The findings show that cue-drinking memory networks can be destabilised by explicitly engendering reward prediction error at recall. This study was funded by an ESRC studentship awarded to RK Das Das

MB26

ACUTE EFFECTS OF ALCOHOL ON SOCIAL OSTRACISM

Moss A, Clinical Psychopharmacology Unit, UCL, Gower St, London WC1E 6BT abbeydaymoss@gmail.com
Buckingham J(1), Lawn W(1), Hindocha C(1), Ralph N(2) Gyure K(1), Curran HV(1), Freeman TP(1) (1)Clinical Psychopharmacology Unit, UCL, Gower St, London WC1E 6BT (2)Research Dept of Clinical, Educational and Health Psychology, UCL, Gower St, London WC1E 6BT

Introduction: Evidence suggests a relationship between social ostracism and alcohol dependence. By using a computer simulation paradigm of a bull throwing game, Cyberball, it is possible to induce the experience of social exclusion. A recent study found that alcohol dependent patients showed altered performance on this task when compared to controls, as measured using fMRI (Maurage et al, 2012, Neuropsychopharmacology, 37, 2067-75). To our knowledge, no previous study has examined the relationship between acute alcohol consumption and social ostracism. The aim of this study was to firstly establish whether social exclusion caused a negative and unpleasant experience, and secondly to ascertain if an acute dose of alcohol influenced this response. Methods: Over two occasions, in a repeated-measures crossover design, a sample of 32 volunteers were given a low dose of alcohol (0.4g/Kg) or matched placebo under double-blind conditions. The mean age of the sample was 22.53 (SD: 4.28). Participants were required to score at least 8 on the Alcohol Use Disorder Identification Test, indicating engagement in hazardous drinking (mean: 14.72, SD: 8.57, range: 8-29). Using Cyberball simulation, participants were exposed to a social inclusion and exclusion event during each session. To measure the effects of exclusion, participants completed the Fundamental Needs Questionnaire after each session, which consists of the following subscales: ‘belonging’, ‘self-esteem’, ‘control’, and ‘meaningful existence’. The dependent variables were analysed by means of 2x2x4 repeated measures analysis of variance, with the within subject factors of exclusion, alcohol, and subscale. Results: As expected and in line with previous literature, exclusion in the Cyberball paradigm led to increased ostracism scores on the Fundamental Needs Questionnaire (F(1,31)=119.607, p<0.001, np2=0.794). An interaction between exclusion and subscale (F(3,93)=14.261, p<0.001, np2=0.315) indicated that exclusion effects were particularly marked for the ‘belonging’ subscale (np2=0.820) although large effect sizes were found for the other subscales of ‘self-esteem’ (np2=0.549), ‘control’ (np2=0.510) and ‘meaningful existence’ (np2=0.699). Administration of alcohol did not influence scores, or interact with effects of exclusion or subscale. Conclusions: This study replicates findings that exclusion using the Cyberball paradigm increases scores on the Fundamental Needs Questionnaire. Contrary to our hypothesis however, there was no mitigation of these effects by alcohol. Future studies could investigate the Cyberball paradigm further by using additional doses of alcohol and other drinking populations. This study received no external funding.
ABSTRACTS

MB27

“WAITING” IMPULSIVITY IN BINGE-DRINKERS: A POTENTIAL RISK FOR DEVELOPING ALCOHOL USE DISORDER?

Mechelmans DJ, Dept. of Psychiatry, Univ of Cambridge, Addenbrooke's Hospital, Level E4, Cambridge CB2 0QQ dm655@cam.ac.uk
Banca P (1) Lange I (1), Worbe Y (2), Irvine M (1), Harrison NA (3), Voon V (1, 2, 4) (1) Dept of Psychiatry, Univ of Cambridge, Addenbrooke’s Hosp, Cambridge CB2 0QQ (2) BCNI, Univ. of Cambridge, Addenbrooke’s Hosp, Cambridge CB2 0QQ (3) Brighton and Sussex Medical School, Univ.of Sussex, Brighton BN1 9PX (4) Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge

Converging evidence implicates heightened substance use disorders and other behavioural addictions (Perry & Carroll, 2008, Psychopharmacology (Berl)(200):1-26; Robbins et al., 2012, Trends Cogn Sci (16): 81-91). Impaired motor inhibition and impulsivity has been advocated as one the underlying cognitive changes directing the transition from alcohol binge to alcohol use disorder (AUD) (Field, Schoenmakers & Wiers, 2008, Drug Alcohol Depend (97): 1-20). Motor inhibition can be divided into (i) motor response inhibition, as measured using the Stop Signal task or the Go/No Go task, or (ii) premature responding or anticipatory responding prior to target onset. Preclinical studies of premature responding using the 5-CSRTT have shown that premature responding and high impulsive choice potentially predicts risk for substance use disorder (Belin et al., 2008). Recently, Voon et al. (2014) Biol Psychiatry (75): 148-155 developed a 4 CSRTT to study premature responding in humans. Here we studied a binge-drinking population stringently defined according the diagnostic criteria for binge-drinking from the National Institute on Alcoholism and Alcohol Abuse. We hypothesized that motor impulsivity would be elevated in binge drinkers compared to healthy volunteers. Motor impulsivity was assessed using the Premature Responding Task, and the Stop-Signal Task. Secondary, exploratory analyses were done on a variety of compulsivity measures. We show that binge drinking subjects have greater premature responding compared to healthy volunteers (T=2.068, p=0.041). No differences were found in the SSRT (GoRT: T=1.259, p=0.212; SSRT: T=0.216, p=0.830). Additionally, no differences were found in measures of compulsivity. Previously, premature responding has been shown in alcohol abstinent subjects and methamphetamine dependence subjects, as well as pathologic video gambling (Voon et al., 2014; Irvine et al., 2013, PLoS One (8): e75914). Unlike (preclinical) literature on other drugs, this is one of the first studies to assess the role of premature responding as a predictor for AUD. Our study in binge-drinkers, a group at high risk to develop AUD, proposes premature responding as a potential biomarker for AUD. These findings support a model favouring (motor) impulsivity as a precursor for compulsivity in behavioural addictions. Research supported by the Wellcome Trust.

MB28

DOPAMINE REGULATES APPROACH-AVOIDANCE IN HUMAN SENSATION-SEEKING

Norbury A, Inst of Cognitive Neuroscience, UCL, 17 Queen Square, London WC1N 3AR agnes.norbury.10@ucl.ac.uk
Kurth-Nelson Z(2,3), Winston JS(1,3), Roiser JP(1), Husain M(4) (1) Inst of Cognitive Neuroscience, UCL, 17 Queen Square, London WC1N 3AR
(2) Gatsby Computational Neuroscience Unit, UCL, 17 Queen Square, London WC1N 3AR (3) Wellcome Trust Centre for Neuroimaging, UCL, 12 Queen Square, London WC1N 3BG (4) Dept of Experimental Psychology & Nuffield Dept of Clinical Neurosciences, Univ of Oxford, Oxford OX1 3UD

Sensation-seeking, or motivation for ‘intense and unusual’ sensory experiences, is a personality trait that constitutes a vulnerability factor for a variety of psychopathologies – particularly gambling and substance addictions. However, sensation-seeking remains underexplored in humans, and little is known about the underlying neural mechanisms. Previously, higher sensation-seeking score has been associated with lower levels of striatal D2-type dopamine receptor availability (Gjedde et al., 2010, PNAS, 107:3870–3875), possibly due to higher occupancy by endogenous dopamine. In order to test this hypothesis, we investigated the effects of attenuating dopaminergic neurotransmission via D2 receptors on a novel instrumental measure of human sensation-seeking. Healthy volunteers (N=30) completed a test in which they were given the opportunity to experience an additional ‘intense’ sensory stimulus (mild electric shock) during performance of economic decision-making task. A simple computational modeling analysis was then applied to derive the economic value (positive or negative) that individuals assigned to the opportunity to receive the additional sensory stimulation (0). Effects of the selective D2 antagonist haloperidol (2.5mg) on behaviour on this paradigm were probed using a within-subjects, double-blind, placebo-controlled design. Under normal conditions, we observed a strong relationship between relative reaction times for shock (CS+) vs non shock-associated (CS-) and 0 value (r=0.602, P=0.001). Specifically, participants who assigned a positive θ value were faster to choose CS+ compared to CS- stimuli (indicative of conditioned approach), and participants who assigned a negative θ value showed the opposite pattern (conditioned avoidance). Crucially, this relationship was abolished under haloperidol (P=0.310; significant decrease in correlation coefficient, P=0.041). Moreover, θ value was positively related to self-reported sensation-seeking score on placebo but not haloperidol (r=0.391, P=0.040; P=0.5). Further analysis revealed that this was due to a selective drug-mediated decrease in θ value in participants who showed an appetitive approach reaction (i.e. speeded relative reaction times) towards CS+ stimuli under normal conditions (i.e. ‘behavioural high sensation-seekers’; repeated-measures ANOVA of 0, drug*group F1,26=10.64, P=0.003; significant decrease in value in the approach, but not avoid group, P=0.009; P=0.1). We found no evidence for any effects of drug treatment on subjective or physical side-effects, general psychomotor function, or learning of the stimulus-shock associations (all P>0.2). These findings provide the first direct evidence of sensation-seeking behaviour being driven by a dopaminergic approach-avoidance-like mechanism in humans, and provide a framework for investigation of various psychopathologies in which extreme sensation-seeking is a risk factor. This research was supported by the Wellcome Trust.
PERINATAL ANXIETY AND DEPRESSION: IDENTIFYING THE WOMEN AT RISK. A REVIEW

Background: Our own prospective work (Pawlby et al. 2009, J Affect Disord,13(3):236-43; Plant et al. 2013, Psychol Med.43(3):519-28) has shown how the offspring of mothers with even mild-to-moderate depression in pregnancy, often co-morbid with anxiety, can be affected throughout their lifetime into adulthood. Method: A systematic literature analysis was performed with the focus on the risk factors for perinatal anxiety and depression. We used the main databases for psychological and medical research, PubMed, PsychINFO, and the Cochrane Library. The following key words were used, as single terms or in combination: perinatal/antenatal/postnatal depression; perinatal/antenatal/postnatal anxiety; risk factor/s; perinatal mental health; perinatal mental disorders; pregnancy; post-partum; maternal sensitivity; child care; screening; assessments; evaluations. In addition, the following sources of grey literature were consulted: NICE guidelines, reports from related charities (for example, Tommy’s) and scientific organizations (for example, Marcé Society) and information on relevant websites. Original papers were included if they were written in English language and published after 1st of January 2000, up to and including unpublished data; while key relevant literature reviews and meta-analyses were included even if published before the 1st of January 2000. After cross-referencing the different sources, and excluding duplicates or irrelevant papers, a final number of 93 papers were selected for further analysis and discussion. Results: Many factors have been found to play a significant role in the onset of anxiety and mood disorders during pregnancy and the postpartum period. The most significant factors are: personal history of depression/anxiety (15 papers); antenatal anxiety/depression (15 papers); lack of social support, and especially of partner support (11 papers); unwanted pregnancy (10 papers); stressful life events before or after pregnancy (9 papers); young age (8 papers); negative cognitive and coping style and low perception of auto-efficacy (8 papers); low income/financial hardship (8 papers); problematic marital relationship and/or domestic violence (7 papers); history of abuse (5 papers); and family history of psychiatric illness (3 papers). Among these factors, woman’s adjustment to motherhood is more difficult if they have experienced abuse or poor care provided by parents, are of young age, are single mothers, have lack of partner support, or have negative cognitive style. Conclusion: The administration of a screening tool that identifies women at risk of both anxiety and depression during pregnancy and the postpartum period should be universal practice in order to promote the long-term wellbeing of mother and baby. Financial sponsorship: National Society for the Prevention of Cruelty to Children (NSPCC)

ESTIMATING CLINICALLY IMPORTANT CHANGE ON THE BECK DEPRESSION INVENTORY: TIME TO RETHINK HOW WE MEASURE DEPRESSION OUTCOMES IN CLINICAL TRIALS?

Introduction: The Beck Depression Inventory (BDI) self-administered questionnaire is widely used in clinical research on depression. However, the minimum clinically important difference (MCID), that is the minimum improvement required to be clinically worthwhile, is unknown. It is also unknown whether the MCID differs according to patient characteristics such as initial depression severity or previous non-response to antidepressant medication. The aim of this research was to estimate the MCID on the BDI according to the patient’s report of feeling better, and to examine whether this estimate varied according to initial severity and previous antidepressant-resistance. Methods: Improvement on “global rating of change” scales were compared with changes in BDI scores using Receiver Operator Characteristics, logistic regression, and Generalised linear models (GLM), in previously collected data (n = 1039) from three large RCTs for the management of depression (GenPod and TREAD) or treatment-resistant depression (CoBalT) in primary care. The cut-point from the ROC analyses provides the optimal threshold (in terms of maximising the sum of sensitivity and specificity) above which individuals are classified as “better” and below which they are classified as “not better”. The ROC analyses therefore provide the best estimates of MCID. GLM analyses were used to explore baseline dependency and to assess whether MCID is best measured in absolute terms (i.e., difference scale) or as percent reduction in scores from baseline (i.e., ratio scale). Results: Improvement in BDI scores associated with reporting feeling “better” depended on initial depression severity with more severe patients requiring a bigger reduction in BDI score in absolute terms to report feeling better. GLM indicated that, given this baseline dependency, the MCID is best measured on a ratio scale. We estimated a MCID of a 17.5% reduction in scores from baseline from ROC analyses. The corresponding estimate for individuals with longer duration depression who had not responded to antidepressants was higher at 32%. Conclusions: MCID on the BDI is dependent on baseline severity and the MCID for longer duration depression that has not responded to antidepressants is larger than that for more typical depression. This has important implications for the design and interpretation of clinical trials and clinical practice. Outcome may need to be assessed in terms of percent reduction in scores from baseline, and greater improvements on the BDI are required to indicate clinically meaningful change in depression which has not responded to antidepressant medication. Funding: This was a secondary analysis of trial data. The original data collection for TREAD and CoBalT was funded by the Department of Health as part of the NIHR Health Technology Assessment programme. GenPod was funded by the MRC. All were supported by the Mental Health Research Network (MHRN), and Primary Care Research Network (PCRN). CoBalT was additionally supported by the Scottish Primary Care Research Network (SPCRN) and Scottish Mental Health Research Network (SMHRN). KB was supported by a MRC studentship.
**MC03**

**WHY DO WE PRESCRIBE ANTIDEPRESSANTS TO DEPRESSED TEENAGERS?**

*Cousins L.*, Dept of Psychiatry Univ of Cambridge, Douglas House Trumpington Rd, Cambridge , CB2 8AH, lesley.cousins@gmail.com


Introduction: Unipolar Major Depression (MD) is a significant health problem within our teenage population with the one month prevalence increasing from 2% in late childhood to 6% in late adolescence. MD during this period is associated with detrimental outcomes including suicide, substance abuse and physical health problems. Depressed teens are also subject to a lifetime course with high rates of relapse. National Institute Clinical Excellence (NICE) suggests that antidepressants are only offered to adolescents with moderate to severe depression after psychological therapies have first been applied. Clinical experience suggests this guidance is not always followed and antidepressants are often prescribed prior to talking therapies taking place, perhaps because the latter are not easily available in many regions. Methods: Improving Mood with Psychoanalytic and Cognitive Therapies (IMPACT) is a multicentre randomised controlled clinical trial of adolescents with MD. The trial is designed to investigate the efficacy of 3 different psychological therapies in reducing the risk of symptomatic recurrence. Of the 464 individuals recruited to the study, 18% were taking serotonin reuptake inhibitor (SSRI) antidepressants at the time of randomisation. In an attempt to elucidate the rationale underlying prescribing before entering the trial, we investigated whether there were clinical differences at randomisation in individuals who had been prescribed from those who had not. Results: Trial participants who had been prescribed antidepressants were significantly more likely to report self-harming behaviours and have lower antisocial behaviour symptoms compared to those not on SSRIs. There was no difference in the severity of depression or levels of personal impairment between the two groups. We noted a significant difference in prescribing rates between research centres with 28% of individuals from East Anglia being prescribed antidepressants compared with 11% and 13% within the London and North West of England populations respectively. However these centre differences did not explain the overall differences in self-harm and antisocial behaviour observed between the SSRI and non-SSRI groups. Conclusion: Our findings suggest that prescribing of SSRIs to depressed teens is based on non-depressive behaviour symptoms. This is not in keeping with NICE guidelines. This work is supported by the National Institute of Health Research UK.

**MC04**

**IDENTIFYING CLINICAL FEATURES OF THE INTERFERON ALPHA INDUCED DEPRESSION SYNDROME: A PRINCIPAL COMPONENT ANALYSIS OF HAMILTON DEPRESSION SCALE SCORES IN A PROSPECTIVE COHORT OF HEPATITIS C TREATED PATIENTS**

*Doherty AE*, BSMS, Univ of Sussex Brighton East Sussex, BN1 9PX, bsm2561@uni.bsms.ac.uk

Rolt M(1,2), Fialho R(1,3), Keller M(4), File A(4), Tibble J(4), Whale R(1,5) (1) Sussex Partnership NHS Foundation Trust, Brighton, BN3 7HZ (2) Univ of Southampton, Highfield Campus, SO17 1BJ (3) Univ of Sussex, School of Psychology, Brighton BN1 9QH (4) Royal Sussex County Hosp, Eastern Rd, Brighton, BN2 5BE (5) BSMS, Brighton, BN1 9PX

Background: Chronic hepatitis C has worldwide prevalence of 160 million with 215,000 cases reported in the UK. Interferon-α plus ribavirin is an established treatment but induces Major Depressive Disorder (MDD) in up to 50% of those exposed. MDD often prompts early treatment discontinuation. Few studies have quantitatively investigated specific features of interferon-α-induced depression. This project aimed to quantitatively explore features of interferon-induced MDD, defined by the Structured Clinical Interview for DSM-IV (SCID-I), using the 21-item Hamilton Depression Rating Scale (HAMD) in a large sample of patients. Methods: Hepatitis C-infected patients due to receive interferon-α treatment were recruited at hepatology clinics. The SCID-I and 21-item HAMD were administered at baseline and 4 weeks during treatment. If SCID defined transition to MDD was recorded, individual HAMD item scores for that time point were documented. Demographic data, previous psychiatric history, HIV co-infection status and hepatitis C virus genotype were recorded. Exclusion criteria were: MDD or anti-depressant use at baseline, previous interferon therapy, transition to MDD during treatment but after starting antidepressants or transition after 6 months after treatment commencement. Standardisation of HAMD scores was achieved through Z-scores using 50% of maximum item score as a benchmark against which to compare item mean averages. Principal Component Analysis (PCA) was used to explore how the 21-item HAMD can be reduced to fewer overarching components, which define the main themes of interferon-induced depression. Results: 138 patients were included, having transitioned to MDD during treatment. HAMD items with positive Z-scores were Somatic symptoms (general) (Z=0.96), Work and activities (Z=0.94), all 3 Insomnia types (middle (Z=0.63), early (Z=0.60) and late (Z =0.53)), Genital symptoms (Z=0.19), Depressed mood (Z=0.11) and Somatic symptoms (gastrointestinal) (Z=0.09). The lowest Z-scores were for Retardation (psychomotor) (Z=−3.84) and Insight (З=−3.57). A 4-factor PCA using 18 items explained 52.8% of variance and revealed the dimensions of interferon-induced depression to be: Physical somatic symptoms, Psychological neurosis symptoms, Sleep disturbance and Unclassifiable symptoms. Conclusions: Interferon-α-induced depression is most clearly characterised by physical somatic symptoms including fatigue and weakness affecting productivity, and sleep disturbance (early, middle and late insomnia). Psychomotor retardation and loss of insight are not common features of this syndrome. Earlier identification of such mood symptom groups may enhance more effective treatment and improvement of discontinuation rates. Further research will quantify differences of HAMD item scores and groupings between non-iatrogenic and interferon-induced depression. Financial support: All authors were supported by their host institutions and Renata Fialho was also part funded by an unrestricted grant from Roche Pharmaceuticals.
MC05

FIXED DOSE COMBINATION (FDC) PRODUCTS IN PSYCHIATRY: SYSTEMATIC REVIEW AND META-ANALYSIS

Farooq S, Dept of Psychiatry Staffordshire Univ UK & Postgraduate Medical Inst, Peshawar, Pakistan, Lady Reading Hospital Peshawar, Pakistan, 75500, sfarooqlrh@yahoo.com
Singh S Black Country NHS Partnership Foundation Trust & Univ of Wolverhampton, UK

Introduction: Fixed Dose Combination (FDC) drugs are preparations that include two or more drugs in fixed proportions in the same formulation. These represent one of the most effective strategies in Medicine and combinations are made both with drugs in different classes and from medicines in the same class. Despite highly prevalent use of combination of different drugs in Psychiatry, FDCs products are not widely available in psychiatry and the evidence evaluating the efficacy of FDC has not been systematically reviewed. We aimed to systematically review the evidence for the use of FDC in mental health. Methods: A systematic search of all major data bases was carried out using suitable search terms for the Fixed Dose Combinations (FDC), defined as combination of two or more drugs used in a fixed dosage and administered as a single oral preparation. Results: We examined 536 abstracts for potentially relevant studies and found 49 articles which could be relevant to the inclusion criteria. We identified 9 double blind randomised controlled trials, which generated 15 comparisons of combination products against single drug or placebo with total sample size of 2827 in all studies. Different combination products were identified but only two combinations were evaluated in double blind trials i.e. Olanzapine plus Fluoxetine and Amitryptiline plus Chlordiazepoxide. All FDCs were significantly superior to a single agent with SMD -0.29 (CI= -0.34 -0.14, P < 0.001) in improving depression. In the subgroup analysis OFC combination was significantly superior to a single therapeutic agent for bipolar depression (SMD -0.32; Cls = -0.45, -0.19; p < 0.001) and for treatment resistant depression (SMD -0.29; Cls = -0.49, -0.08; p < 0.005) but not for Borderline Personality and Major Depressive Disorder. No study reported on the cost effectiveness and only two studies reported on compliance which was not significantly different between any treatment group. Conclusion: This is the first systematic review and meta-analysis of combination products in psychiatry. In clinical practice use of add-on medicine is rule rather than the exception in psychiatry but the evidence for the effectiveness of combination products is practically limited to one combination of two or more drugs used in a fixed dosage and administered as a single oral preparation with total sample size of 2827 in all studies.

MC06

S DEPRESSION “UNDERRECOGNISED AND UNDERTREATED” IN HAEMODIALYSIS PATIENTS?

Guirguis A, Renal Dept and Centre for Lifespan and Chronic Illness Research. Health and Human Sciences, ENT Herts NHS Trust and Univ of Hertfordshire, College Lane, Health Research Bldg, Room 1F424, AL10 9AB, a.guirguis3@herts.ac.uk
Guirguis A 1, 2, Friedli K 2, Fineberg NA 2, 3, Davenport A 5, Davenport A 5, Da Silva- Gane M 2, Chilcot J 7, Wellsted D 2, Farrington K 1, 2 1East and North Hertfordshire NHS Trust, 2Univ of Hertfordshire, 3Hertfordshire Partnership Univ NHS Foundation Trust, 4Univ Hospitals Birmingham NHS Foundation Trust, 5Southend Univ Hospital NHS Foundation Trust, 6Royal Free London NHS Foundation Trust, 7King’s College London

AIMS: To recognise the degree to which depressive symptoms in End Stage Renal Disease (ESRD) patients undergoing haemodialysis (HD) are recognised and treated or not. BACKGROUND: Depression is often said to be unrecognized and under-treated (Hirschfeld et al. The National Depressive and Manic-Depressive Association consensus statement on the under treatment of depression. 1995. JAMA; 277(4):333-40) in patients with chronic medical illness leading to negative outcomes. Part of the problem may be symptom overlap between depression and uremia. Prevalence estimates of depression in this population vary widely from 15% to 69%. Depressive symptoms in ESRD may negatively affect general health awareness mortality rate, treatment adherence and inpatient hospitalisation (Kimmel et al. Psychiatric illness in patients with end-stage renal disease. 1998. Am J Med;105(3):214-21). It is therefore an important health issue in this population. METHODS: We studied all haemodialysis patients at 3 renal centres across England. Inclusion criteria were; having been on dialysis >3 months, >18years of age and being able to read and speak English. All eligible patients were screened for depression using Beck Depressive Inventory Version II (BDI-II). Medication status was obtained by patients self-reports and medical records. RESULTS: In 480 HD patients (Male 310 (64.6%) mean age was 64.2 ±16.1 years. The mean BDI-II was 13.6, ±11.3. Of these, 168 patients (35%) scored ≥ 16 on the BDI-II representing moderate depressive symptomatology. They were younger than the non-depressed sub-group (mean age 60.6 v 66.1 years: p = 0.004). 89 patients (18.5% of the whole HD group) were already taking antidepressants-25 of 312 patients with low BDI (8.1%) and 64 of 168 with high BDI (38%). In those with high BDI-patients taking antidepressants had a higher mean BDI score (30.6 ± 10.4 v 25.0 ± 7.2: p< 0.001) than untreated patients. They tend to be younger (55.9 SD 16.6 v 62.2 SD 16.5 years: p = 0.081) but appeared to be similar with respect to gender, ethnicity, marital status, educational background, dialysis vintage or comorbidity. They had higher median scores in the BDI domains of worthlessness, past failure, and suicidal thoughts (p < 0.01 in all cases). CONCLUSION: >1/3 HD patients had BDI-II ≥ 16 concordant with moderate depressive symptomatology. Antidepressants were commonly prescribed in this group and those taking antidepressants had high depressive symptomatology compared to their untreated counterpart, questioning the value of antidepressants in this cohort. This is contrary to many previous findings which suggest that depression is under-diagnosed and under-treated in this population. Prospective studies are required to investigate the diagnosis and management of depression in HD patients. FUNDER: National Institute of Health Research, Research for Patient Benefit.
PERINATAL ANXIETY AND DEPRESSION: A REVIEW OF EFFECTIVE ‘LIGHT-TOUCH’ PREVENTATIVE INTERVENTIONS

Howells HG, Dept of Perinatal Psychiatry Inst of Psychiatry, 16 De Crispigny Park, Denmark Hill London, SE5 8AF, hedie.1.howells@kcl.ac.uk
Biaggi A(1), Conroy S(1), Pawlby S(2), Pariante CM(2) Dept of Perinatal Psychology, Kings College London, Inst of Psychiatry, 16 De Crispigny Park, Denmark Hill, London, SE5 8AF Dept of Psychological Medicine, Kings College London, Inst of Psychiatry, Room 2-055, The James Black Centre, 125 Coldharbour Lane, London, SE5 9NU

Background: Perinatal depression and anxiety are significant health concerns, affecting around 13% of women (Dennis et al., 2009, BMJ, 338, a3064). The ‘long shadow’ cast by poor perinatal mental health is well documented and emphasizes consequences for the child which can present as various negative outcomes such as poor emotional welfare, unachieved social roles, antisocial behaviour and substantial financial strains on society (Hay, et al., 2010, Child Development, 81(1), 149-165). Our own work has identified both clinical and biological mechanisms through which such psychopathology is transmitted from mothers to children (Plant et al., 2013, Psychological Medicine, 43, 519-528; Hay et al., 2008, Journal of Child Psychology and Psychiatry, 49,1079-1088). Identifying interventions that work by reducing stress and therefore minimizing the activation of the stress hormones and preventing the onset of perinatal mood disorders is a priority in translating our findings from the laboratory to pregnant women. This review aims to provide a pragmatic resource that outlines the recent literature and developments in interventions that can be administered in the community, some by non-health professionals, to prevent and alleviate mild-to-moderate perinatal depression and anxiety. Method: A review of recent, relevant literature was conducted within the main archives of psychological and medical research: PubMed, PsychINFO and EBSCOhost, as well as various other, (informal) sources. Particular attention was given to interventions that can be delivered by non-health professionals, variables that may modify the efficacy of interventions and those that target individuals other than the mother. Results: Various interventions were found to be effective in the prevention and alleviation of mild-to-moderate perinatal anxiety and depression. These include therapeutic interventions such as ‘interpersonal therapy’ and ‘cognitive-based therapy’, as well as complementary therapies such as light-box therapy and holistic approaches. Supportive interventions are notably effective and can take the form of group support, web forums and organized and unstructured peer and social support. Educational and informative interventions such as policy guidelines are also found to be efficacious and it could be argued that they deliver support and therapy. All these interventions are discussed in the light of demographic considerations such as socio-economic status, technology accessibility, disability and reflections on culture. Conclusion: The established consequences of perinatal anxiety and depression benefit research on remedial and preventative interventions. We need to be aware of factors that can potentially hinder the efficacy of interventions when evaluating them. Funding: NSPCC (National Society for the Prevention of Cruelty to Children)

ACTigraphic features of inter-episode bipolar affective disorder: a systematic review and meta-analysis

Quested DJ, Psychiatry, Oxford Health NHS F Trust/ Univ of Oxford , Warneford Hospital, Oxford, OX3 7JX, digby.quested@psych.ox.ac.uk

Bipolar disorder has been widely studied using actigraphy, but the data from single studies have yet to be collated in order to summarise the relevant findings. We undertook a search and quantitative data analysis on studies using actigraphy to detect changes in activity and sleep pattern in bipolar patients when euthymic, compared to controls. A comprehensive literature search of the PubMed/MEDLINE, Cochrane Library, CINHAL and PsycINFO databases was carried out and the search was updated to March 2014. The primary outcome measures were analyses of ‘sleep duration’ and ‘activity mean’: As secondary outcomes we analysed ‘sleep onset latency’, ‘sleep efficiency’, and ‘time awake after sleep onset’. Data were extracted and analyzed using a conservative model and expressed as standardized mean difference (SMD). Eleven studies comprising 759 subjects met quality criteria for inclusion. The results show a significant and moderate effect of sleep reduction in patients versus controls (SMD = 0.62 [0.34, 0.91]) and a significant and large effect in the decrease of activity mean (SMD = -0.94 [-1.49, -0.40]). The secondary outcome measures were all significant and show an altered pattern of sleep in bipolar disorder patients even when relatively well. Results from the subgroup analyses further support sleep variability in between more overt episodes of relapse. The findings therefore provide a measure of support for the growing use of actigraphy in bipolar affective disorder as a technique involving more objective measurement of activity and sleep parameters. It is also generally clinically acceptable for patients and will likely enable improved delineation of mood instability in future studies. The final objective then becomes possible - linking objectively measurable parameters as valid and reliable proxies for symptomatic deterioration in a manner which enables improved treatment or related investigation. Funding through Oxford Health NHS F Trust R and D.
MC09
MAINTENANCE TREATMENT WITH REPEATED KETAMINE OF 8 PATIENTS WITH TREATMENT RESISTANT DEPRESSION
McShane R, ECT Oxford Health NHS Foundation Trust, Warneford Hospital Warneford Lane Oxford, OX3 7JX, peter.diamond@oxfordhealth.nhs.uk
Diamond PR (1) (1) Oxford Health NHS Foundation Trust, Oxford, UK

Background: There is no known strategy for maintaining the initial antidepressant response of ketamine infusions. Case series have reported some success in using repeated ketamine. Methods: We report 8 patients who initially responded to a course of ketamine infusions and then received either further courses of infusions following relapse, regular infusions as part of a planned maintenance strategy, or both. All treatment plans were individualised due to the varying length of response duration. Mood was tracked using TrueColours monitoring system, sending either email or SMS prompts to patients to complete the Quick Inventory of Depressive Symptomology (QIDS), with responses captured on a remote computer system. Urinary symptoms were also monitored over this period using self report measures. Results: The time course of response was highly variable. Some patients (3/8) had prolonged responses lasting several months to 1-2 more courses of ketamine following relapse. One patient with less severe illness was maintained for 6 months with single intermittent prophylactic infusions prior to the expected relapse date. 2/8 patients became refractory to ketamine treatment with 5/8 appearing to show diminished responses to subsequent infusions. A single patient who remained well for 4 months following each of 3 courses eventually became refractory to ketamine, but then responded slowly to a course ECT and had a response to a second course of ECT which was unaltered by use of ketamine as the anaesthetic. No patient experienced any symptoms indicative of interstitial cystitis. Conclusion: Ketamine played a useful part in the management of these complex, otherwise treatment resistant, patients. Since subjective accounts of past illness are coloured by mood, consistent long term monitoring is a useful adjunct in management. Funding This article presents independent research supported by both the National Institute for Health Research under its Research for Patient Benefit Programme (grant number PB-PG-0408-16030) and the Oxford Health NHS Foundation Trust.

MC10
TRANSCRANIAL DIRECT CURRENT STIMULATION (tDCS) IN DEPRESSION: SYSTEMATIC REVIEW AND META-ANALYSIS
Meron D, Unv Dept of Psychiatry, Univ of Southampton Faculty of Medicine, College Keep, 4-12 Terminus Terrace, Southampton, SO14 3DT, dan@soton.ac.uk
Hedger NAA (1), Garner M (1, 2), Baldwin DS (2, 3) (1) School of Psychology, Faculty of Social and Human Sciences, Univ of Southampton, Southampton; (2) Clinical and Experimental Sciences, Faculty of Medicine, Univ of Southampton, Southampton; (3) Unv. Dept of Psychiatry and Mental Health, Univ. of Cape Town, South Africa

Introduction: Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation (‘neuromodulatory’) modality, which has been evaluated in treating depressed patients. We report findings of a meta-analysis of tDCS in depression, which includes the more recent literature, significantly increasing the number of subjects analyzed; uses a methodology combining dichotomous and continuous outcome measures; and performs moderator analyses to clarify the effect of putative moderators as identified in an earlier narrative analysis (Meron D et al. J Psychopharmacol 2013; 27 (suppl.): A49). Method: Literature search and subsequent meta-analysis for all randomized controlled trials in clinical populations with diagnoses of depressive (unipolar and/or bipolar) or anxiety disorders. For continuous treatment effects the primary effect size index was Cohen’s d (the difference between active and sham tDCS in mean reduction in depression severity rating scale scores, divided by their pooled standard deviation). For each study, we computed d and 95% confidence intervals using independent samples t, p and F statistics, using the Comprehensive Meta Analysis Software (CMA: Biostat, Englewood, NJ). For categorical treatment effects, response and remission rates in active and control treatment groups were compared using the log odds ratio (LOR) as an effect size index. For moderator variables we assessed the impact of potential categorical and continuous moderators of the estimates of treatment effect. Results: Continuous treatment effects: the combined treatment effect was significant and consistent with a medium effect size (k=9, d=0.57, 95% CI=[0.22, 0.92], p<.001). The test for heterogeneity was significant (Q = 16.985, df = 8, p =.003): 53% of the heterogeneity between studies could not be accounted for by sampling variability, justifying the use of a random effects model. The ‘fail safe’ calculation (using the Rosenthal approach) indicated that 71 unpublished studies averaging null results would be required in order for the treatment effect to dip below significance. Moderator analysis: for continuous outcomes, meta-regression indicated the only significant moderator of treatment effect was use of concurrent antidepressants, the treatment effect being significant only in antidepressant-free samples. The difference between patient groups with or without antidepressants was significant, (QM(1)= 4.80, p=.028), 61% of the total heterogeneity among treatment effects being explicable by this factor. Categorical treatment effects: the pooled LOR did not reach significance, for either response (p=0.116) or remission (p=0.589). Discussion: tDCS represents an effective treatment option in patients with major depression, and is a potentially useful alternative to antidepressant. In depressed patients with low level of treatment resistance, tDCS offers comparable acute phase efficacy to fluoxetine, but with a potentially earlier onset. Current evidence does not support the use of tDCS as monotherapy in patients with treatment-resistant depression, or as an augmentation approach in those who have not achieved remission with antidepressants. Funding support: none.
MC11
TREATMENT PATHWAY IN BIPOLAR DISORDER

Patel R, Dept of Psychosis Studies, King’s College London, Box PO 63 De Crespigny Park, Denmark Hill, London, SE5 8AF, bap@rpatel.co.uk
Shetty H(2), Boydell J(1), McGuire P(1), Taylor M(1) (1) Dept of Psychosis Studies, King’s College London, Box PO 63, De Crespigny Park, Denmark Hill, London SE5 8AF (2) South London and Maudsley NHS Foundation Trust, Biomedical Research Centre Nucleus, Mapother House, De Crespigny Park, Denmark Hill, London SE5 8AF

Introduction: Bipolar disorder accounts for a significant burden of illness amongst affected individuals and is characterised by sustained periods of depressed and/or elevated mood associated with impaired social functioning. Medications including antipsychotics, lithium and anticonvulsants are used to treat bipolar disorder and prevent relapses. The optimum treatment for an affected individual depends on several factors including polarity of illness (i.e. mania or depression). A cohort study was performed in a large provider of secondary mental healthcare to investigate which medications were most frequently prescribed amongst patients with bipolar disorder, how medication prescriptions related to polarity, and the extent to which patients switch between different medications. Methods: Source of clinical data: SLaM (South London and Maudsley NHS Trust) BRC (Biomedical Research Council) Case Register. The BRC Case Register comprises anonymised electronic health records of individuals receiving care from SLaM. Data from 1,300 patients (meeting the criteria below) was extracted using the Clinical Record Interactive Search Structured Query Language tool (CRIS SQL): (i) Age: 16 – 65 years (ii) First referral to SLaM between 01/01/2007 and 31/05/2012 (iii) Diagnosed with bipolar disorder (iv) Started on a second generation antipsychotic, anticonvulsant or lithium Medication prescriptions following referral were recorded and entered into a Sankey diagram to track medication prescriptions during the course of treatment. A multinomial logistic regression analysis was performed to investigate which medications were most likely to be prescribed for patients depending on polarity. Results: The most frequently prescribed 1st line treatments were second generation antipsychotics (61.6%), followed by sodium valproate (13.5%), lithium (12.1%), lamotrigine (10.5%) and carbamazepine (2.3%). However, over time, patients were increasingly prescribed sodium valproate, lithium and lamotrigine. Patients with mania were more likely to be prescribed a second generation antipsychotic (odds ratio 5.36, 95% CI 2.67-10.8, p<0.001) while patients with depression were more likely to be prescribed lamotrigine as first line treatment (odds ratio 2.20, 95% CI 1.05-4.62). Conclusion: The majority of patients with bipolar disorder were first started on a second generation antipsychotic. However, many of these patients were subsequently started on lithium or an anticonvulsant. Mania was most frequently first treated with an antipsychotic and depression with lamotrigine. These findings suggest that mood stabilising medications are appropriately prescribed in line with current treatment guidelines recommended by the British Association of Psychopharmacology. However, further study is needed to establish the treatment gap for bipolar disorder and the factors associated with this. Funding: MRC Clinical Research Training Fellowship

MC12
FOLIC ACID SUPPLEMENTATION FOR PREVENTION OF MOOD DISORDERS IN YOUNG PEOPLE AT FAMILIAL RISK: A RANDOMISED, DOUBLE BLIND, PLACEBO CONTROLLED TRIAL

Sharpley AL, Dept of Psychiatry, Univ of Oxford, Neurosciences Bldg, Warneford Hospital, Oxford, OX3 7JX, ann.sharpley@psych.ox.ac.uk

Introduction: Clinical mood disorders often become clinically manifest in the later teenage years and early twenties and can be associated with a poor long-term prognosis. The primary prevention of these disorders would therefore have great public health value. Nutritional supplements are a feasible intervention for primary prevention and several epidemiological studies have indicated links between low folate status and depressive symptomatology in the general population. Method: A randomised, double blind, parallel group, placebo-controlled trial in which participants, aged 14-24 years, at increased familial risk of mood disorder, were randomised to folic acid (2.5mg daily) or identical placebo liquid for a maximum of 36 months. Randomisation and primary outcome data were collected from 112 participants; active, n=56 (39 female, mean time in study 23.2 ± 10.0 months, range 4-36 months); placebo, n=56 (39 female, mean time in study 20.0± 12.9 months, range 1-36 months). The groups were well matched for demographic and psychosocial data. Twelve participants in each group had a parent with bipolar disorder; the remaining affected parents had recurrent major depression. Results: The incidence of mood disorder in the folic acid and placebo groups were 14.3% and 17.9% respectively, a non-significant difference. Our data showed that there was no significant difference in survival time between the folic acid and placebo groups (Log Rank (Mantel-Cox) Chi-Square 0.676; df 1, p= 0.41). However, a post-hoc analysis showed that in the 18 patients who reached the primary endpoint, the median time to the onset of the mood disorder was 5 months in the placebo group and 15.5 months in the folic acid group (p= 0.023, Mann-Whitney U test). In keeping with previous studies, the participants who became depressed were found at baseline to have higher scores on the Eysenck Personality Questionnaire-Neurotic subscale) and Responses Style Questionnaire and lower scores on the Children’s Attributional Style Questionnaire-Revised. Conclusions: Although long-term folic acid supplementation was well tolerated, with high levels of adherence, there was no evidence that it reduced the incidence of mood disorder compared to those taking placebo. It was noteworthy that a number of psychosocial risk factors, previously reported to be associated with the development of depression, were more frequent in the subgroup of participants who did go on to experience clinical mood disturbance subsequently. Sources of Support: The study was funded by a research grant from the Stanley Medical Research Institute. Rosemont Pharmaceuticals Ltd. supplied folic acid free of charge.
MC13
ANTIGLUCOCORTICOID AUGMENTATION OF ANTIDEPRESSANTS IN DEPRESSION: THE ADD STUDY
Watson S, ION Newcastle Univ, Wolfson Research Unit, NE4 5PL, stuart.watson@ncl.ac.uk

Introduction: Treatment refractory depression (TRD) is relatively common. Induced or endogenous HPA axis dysregulation is a poor prognostic indicator and in preclinical data attenuates the forebrain 5-hydroxytryptamine response to SSRIs. Antiglucocorticoid strategies include augmentation with the cortisol synthesis inhibitor, metyrapone which improved outcome in one RCT in hospitalised TRD patients (Jahn 2004). The Antiglucocorticoid augmentation of anti-Depressants in Depression (ADD Study) is a multicentre randomised placebo controlled trial of metyrapone augmentation of serotonergic antidepressants in patients with TRD in the NHS. Methods: 165 patients with moderate to severe TRD aged 18 to 65 recruited from primary and secondary care were randomised to metyrapone (500mg twice daily or placebo for three weeks) augmentation of current serotonergic antidepressants. The primary outcome was improvement in Montgomery-Åsberg Depression Rating Scale (MADRS) score five weeks after randomisation (2 weeks after cessation of drug). Secondary outcomes include safety, tolerability and the persistence of any treatment effect. Sub-studies investigating the potential mechanism of action of metyrapone which are not reported here. Results: There were no serious adverse events attributable to the drug and adverse events were the same as with placebo. The estimated mean differences in change scores comparing treatment and placebo groups at five weeks post randomisation (controlling for variation between centres and primary or secondary care origin) were (metyrapone-placebo) MADRS, -0.51(95%CI:-3.48, 2.46); Beck Depression Inventory (BDI), -2.65(95%CI:-6.41, 1.10); Clinical Anxiety Scale (CAS), -0.46(95%CI:-1.20, 2.12); State Trait Anxiety Inventory, 1.2(95%CI:-0.6, 3.0). The differences were not statistically significant. There were also no significant effects seen at 6 months. Discussion The broad inclusion criteria resulted in a representative sample of NHS TRD treated patients. Metyrapone augmentation of antidepressants is not efficacious for moderately depressed patients in outpatient clinics and in the community who have failed to respond to at least two antidepressants. The lack of benefit from metyrapone treatment extended to secondary outcomes such as the CAS and the BDI. The lack of response contrasts with the Jahn study and may reflect the different populations studied - the ADD population included community patients with significant poor prognostic indices including chronicity, neuroticism, early adversity and anxiety. Trial Registration The study was registered on 21/12/2009 (ISRCTN45338259) under the title “Antiglucocorticoid augmentation of antiDepressants in Depression: the ADD study”. Funding details This study was funded by NIHR EME (funder’s reference 08/43/39).

MC14
THE RELATIONSHIP BETWEEN CHILDHOOD ADVERSITY, RUMINATION AND NEUROCOGNITIVE PERFORMANCE IN CURRENTLY DEPRESSED PATIENTS WITH BIPOLAR DISORDER
Clark JE, Academic Psychiatry Newcastle Univ, Wolfson Research Centre, Campus for Ageing and Vitality, Newcastle upon Tyne, NE4 5PL, j.e.clark1990@gmail.com
Gallagher P(1), Porter, RJ(2), Young, AH(3), Ferrier IN(4), Watson S(4) (1) Inst of Neuroscience, Newcastle Univ, The Henry Wellcome Bldg, Framlington Place, Newcastle upon Tyne, NE2 4HH, UK (2) Dept of Psychological Medicine, Univ of Otago, Christchurch, New Zealand, (3) Dept of Psychological Medicine, Inst of Psychiatry, King’s College London, Denmark Hill, London SE5 8AF (4) Academic Psychiatry and Regional Affective Disorders Service, Newcastle Univ, Wolfson Research Centre, Campus for Ageing and Vitality, Newcastle upon Tyne, NE4 5PL, UK

Introduction: Neurocognitive impairment is common in bipolar disorder. Higher levels of self-reported childhood adversity and rumination have also been reported though their relationship to neurocognitive performance is unclear. We examined the relationship between these variables and their role in neurocognitive impairment in bipolar disorder. Method: 60 currently depressed patients with bipolar disorder and 55 healthy controls completed a battery of neurocognitive tests as well as the ruminative responses scale (RRS), the childhood trauma questionnaire- Short Form (CTQ-SF), the Beck Depression Inventory (BDI) and two self-rated measures of neurocognitive abilities; the everyday memory questionnaire (EMQ) and the cognitive failures questionnaire (CFQ). We first compared group scores on the RRS, EMQ and CFQ using independent samples t-tests. We then constructed two path models describing the relationship between outcome measures in patients and controls. All P values were set at .05. Results: Patients had significantly higher total scores on the RRS, EMQ and CFQ as well as all subscales. The path model in patients showed that CTQ-SF and BDI scores directly and negatively impacted pattern span, whilst the direct effect of RRS score on pattern span was positive. RRS score also strongly predicted BDI score and exerted a negative effect on pattern span that was mediated via BDI. The model accounted for a significant proportion of variance in pattern span. Rumination was also strongly linked to lower self-rated cognitive ability and this effect was also mediated by BDI score. In controls, a higher CTQ-SF score predicted poorer forward digit span and higher RRS scores. A higher BDI score also predicted higher CFQ scores. None of these effects were mediated through other outcome measures. Conclusions: The aetiology of neurocognitive impairment in bipolar disorder was explored using path analysis. We found a general relationship whereby rumination exerted positive direct effects on neurocognitive performance and simultaneous negative effects mediated through depression severity. This supports the conception of rumination as a vehicle for goal attainment in the face of perceived failure. The finding that CTQ-SF scores affected neurocognitive performance directly in both patients and controls supports the interpretation of childhood adversity as a transdiagnostic predictor of impairment. Future research should seek to establish the biological basis of our results, which may also be useful in the development of psychological therapies in bipolar disorder. This study was funded by the Stanley Medical Research Institute (REF: 03T-429) and the Medical Research Council
MC15

THE ROLE OF LIFE STRESSORS IN IDENTIFYING GENETIC RISK FACTORS FOR DEPRESSION

Juhasz G, Dept of Pharmacodynamics, Semmelweis Univ, Budapest, Nagyvárad ter 4, Hungary, 1089, gabriella.juhasz@manchester.ac.uk


Introduction: Major depressive disorder (MDD) is one of the most disabling conditions in the world and the WHO predicts that depression will impose the second greatest burden of disease worldwide by 2020. Although about 30-40% of the risk originates from genetic factors hypothesis free genome wide association studies could not provide significant hits so far. One explanation for this negative finding could be that MDD is a heterogeneous disorder both at genetic and phenotypic level. Previous studies demonstrated that environmental stressors, such as childhood maltreatments or recent negative life events, are strong risk factors for depression but their effects are dependent on the vulnerability of the subjects which is most likely determined by specific genetic variants. Methods: In the present study we investigated genetic variants in the galanin system in relation to life stressors because of the strong biological evidence of its stress modulating effects. We used the NewMood population cohort (n=2361 from Manchester and Budapest) to carry out state of the art gene-environment interaction analysis on depression-related phenotypes (reported lifetime depression, Brief Symptom Inventory depression and anxiety scores) and then test the relevance of specific genes in these phenotypes in the highly stressed group compared to those who had mild or moderate stress. Results: Our results demonstrated that out of the 12 tested genetic variants (SNPs in the galanin system) 7 showed nominally significant gene-environment interactions (p<0.05) despite their disparate genomic locations. Further analysis showed that genes of galanin (GAL) and its receptors (GALR1, GALR2 and GALR3) are more relevant (log posterior probability ratio >3) in the high stress subgroup compared to the mild or moderate stress subgroup. Conclusions: Studies using environmental stressors to investigate the genetic risk of depression further support that MDD is a heterogeneous disorder and that selecting subjects with high life stresses allows delineation of specific biological pathways associated with depression. In addition, the identification of susceptible subgroups for depression would provide a prospect to reduce the specific risk factors to those most likely affected by this disorder. The study was supported by: NewMood (LSHM-CT-2004-503474); NIHR Manchester Biomedical Research Centre; TAMOP-4.2.1.B-09/1/KMR-2010-0001 (Hungary); MTA-SE Neuropsychopharmacology and Neurochemistry Research Group (Hungary); Hungarian Brain Research Program (KTIA_13_NAP-A-II/14) and National Development Agency (KTIA_NAP_13-1-2013-0001); Bolyai Scholarship of the Hungarian Academy of Sciences (X.G.); Swedish Research Council, Karolinska Institutet; NARSAD; Wallenberg Foundations.

MC16

ASSOCIATIONS OF CANNABIS AND CIGARETTE USE AT 16 WITH DEPRESSION AT AGE 18: FINDINGS FROM THE AVON LONGITUDINAL STUDY OF PARENTS AND CHILDREN

Gage S, MRC Integrative Epidemiology Unit, Univ of Bristol, Oakfield House, Bristol, BS8 2BN, suzi.gage@bristol.ac.uk

Hickman,M(1), Heron, J(1), Munafö, M(1), Lewis, G(2), MacLeod, J(1), Zammit, S(3) (1)Univ of Bristol, Bristol, UK; (2)UCL, London, UK; (3) Cardiff Univ, Cardiff, UK

INTRODUCTION: Cannabis use, tobacco use and depression are all associated with each other, but causal relationships are hard to assess. We aim to investigate the relationship between adolescent cannabis and tobacco use with later depression, while attempting to account for the effects of confounding and reverse causation. METHODS: Data from ALSPAC, a prospective longitudinal cohort study based in Bristol, UK, were used. Cannabis and cigarette use were measured at age 16 via questionnaire. Depression was assessed at age 18, using the CIS-R computerised interview. Logistic regression was used to investigate associations between cannabis or cigarettes and depression, before and after adjustment for pre-birth, childhood and adolescent confounders. Our sample size was 1791 participants (57% female). RESULTS: Cannabis use and depression were associated in the unadjusted relationship (OR 1.51, 95% CI 1.23-1.84). Adjustment for pre-birth and childhood confounders did not attenuate the relationship greatly. Nor did further adjustment for cigarette use, or other illicit drug use. Adjustment for alcohol slightly attenuated the relationship (OR 1.38, 95% CI 1.07-1.77). Cigarette use and depression were also associated (OR 1.35, 95% CI 1.11-1.64). Adjustment for pre-birth and childhood confounders attenuated the results only marginally, but further adjustment for cannabis use fully attenuated this association (OR 0.93, 95% CI 0.71, 1.22). Adjustment for alcohol or other illicit drugs also attenuated the findings, but not to the same degree as adjusting for cannabis did, though CIs still crossed the null. CONCLUSIONS: The association between cannabis and depression was robust to all confounding by measured variables, although alcohol led to some attenuation. Associations of tobacco use showed a different pattern, where adjustment for cannabis use, illicit drug use or alcohol attenuated the association. Tobacco and cannabis use are collinear, which makes teasing out independent effects hard. Complementary methods are required to robustly examine independent effects of cannabis and tobacco on depression. Suzanne Gage’s PhD is funded by the MRC. ALSPAC is funded by the MRC and Wellcome Trust.
MC17

SERUM INTERLEUKIN 6 AND C-REACTIVE PROTEIN IN CHILDHOOD AS PREDICTORS OF DEPRESSION AND PSYCHOSIS IN YOUNG ADULT LIFE: A POPULATION-BASED LONGITUDINAL STUDY

Khandaker GM, Dept of Psychiatry, Univ of Cambridge, Box 189, Level E4 Cambridge Biomedical Campus, Cambridge, UK, CB2 0QQ, gmk24@medschl.cam.ac.uk

Pearson RM(1), Zammit S(2), Lewis G(3), Jones P(4) (1) School of Social & Community Medicine, Univ of Bristol, Oakfield House, Oakfield Grove, Bristol BS8 2BN (2) Inst of Psychological Medicine and Clinical Neurosciences, Cardiff Univ, Hadyn Ellis Bldg, Mandy Rd, Cathays, Cardiff, CF24 4HQ (3) Div of Psychiatry, Univ College London, 67-73 Riding House St, London W1W 7EJ (4) Dept of Psychiatry, Univ of Cambridge, Herschel Smith Bldg, Robinson Way, Cambridge Biomedical Campus, Cambridge CB2 0SZ

Introduction: Accumulating evidence suggest a role of cytokine mediated communication between the immune system and the brain in the pathophysiology of depression and psychotic disorders. This is supported by meta-analyses reporting increased serum interleukin (IL) 6 and C-reactive protein (CRP) in first episode psychosis, acute psychotic relapse, and in depression. However, longitudinal studies of systemic inflammatory markers and subsequent psychosis are lacking, and those of depression are limited in number with inconsistent results. In a longitudinal design, we predicted that higher levels of systemic inflammatory markers in childhood would be associated with future risks of depression and psychosis. Methods: The sample included approximately 4500 individuals from the general population-based Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort. IL-6 and CRP were measured in non-fasting serum obtained at age 9 years, excluding those with current infection. At age 18 years, depression was measured in two ways: a clinical interview and a questionnaire so as to allow internal replication. Psychotic experiences (PE) and psychotic disorder were measured by a semi-structured interview. Logistic regression calculated odds ratios (OR) for psychiatric outcomes at age 18 years among individuals in the middle and top, compared with bottom third of IL-6/CRP distribution at age 9 years. Age, sex, body mass index, ethnicity, social class, past psychological and behavioural problem, and maternal post-natal depression were included as potential confounders. Results: At age 18 years, based on interview data. 423 participants met criteria for depression (17.2%), 101 reported PE (4.0%), and 35 met criteria for psychotic disorder (1.4%). Participants in the top third of IL-6 values at age 9 years, compared with those in bottom third were more likely to develop depression at age 18 years; adjusted OR 1.55 (95% CI 1.13-2.14). The risks of PE and of psychotic disorder at age 18 years were also increased with higher IL-6 at baseline; adjusted OR 1.81 (95% CI 1.01-3.28), and 2.40 (95% CI 0.87-6.62), respectively. Moreover, the associations between serum IL-6 at age 9 years, and depression and PE at age 18 years were consistent with linear, dose-response relationship. The results remained virtually unchanged using the questionnaire measure of depression. Conclusions: Higher levels of IL-6 in childhood are associated with risk of depression and psychosis in young adult life. Processes in the inflammatory pathway may be therapeutic targets for these disorders. Inflammation might explain the high comorbidity between cardiovascular disease, diabetes, depression and schizophrenia.

Background: Exposure to childhood maltreatment is associated with dysregulation in the hypothalamic-pituitary-adrenal (HPA) axis, with some studies demonstrating hypercortisolemia and others demonstrating a blunted cortisol response. In this study we investigate the relative impact of exposure to childhood maltreatment and concurrent depression on adulthood cortisol levels. Methods: The sample comprised 103 offspring from the South London Child Development Study (SLCDS), a prospective longitudinal birth cohort study set up in 1986 that has followed mothers and their offspring from pregnancy to 25 years. Data on offspring exposure to childhood maltreatment (birth to 17 years), offspring adulthood depression and offspring adulthood cortisol levels was obtained through one-to-one clinical interview. Results: There was a significant main effect for cortisol levels at 30 minutes post-awakening, F[3, 65] = 3.4, p = .021. Post hoc analyses revealed that adults exposed to childhood maltreatment but who were not depressed in adulthood had significantly higher 30-minute cortisol (mean difference = 4.2, SE = 1.5, p = .024) compared to those who were non-depressed and non-maltreated, and in comparison to those maltreated and also depressed (mean difference = 5.0, SE = 1.7, p = .021). These data suggest hyperactivity in the cortisol response system amongst maltreated (but not depressed) offspring, and that the experience of depression in conjunction with childhood maltreatment leads to blunting of the cortisol awakening response. Conclusions: These findings demonstrate that exposure to childhood maltreatment has effects on the HPA axis that persist into young adulthood which are modulated by the presence of depressive psychopathology. Financial Support: Psychiatry Research Trust, MRC UK

MC18

EFFECTS OF CHILDHOOD MALTREATMENT ON CORTISOL LEVELS IN YOUNG ADULTHOOD

Plant DT, Psychological Medicine, Inst of Psychiatry, King’s College London, 2-059 James Black Centre 125 Coldharbour Lane, SE5 9NU, dominic.plant@kcl.ac.uk

Pariante CM (1), Pawlby S (1) (1) Dept of Psychological Medicine, Inst of Psychiatry, King’s College London

Background: Exposure to childhood maltreatment is associated with dysregulation in the hypothalamic-pituitary-adrenal (HPA) axis, with some studies demonstrating hypercortisolemia and others demonstrating a blunted cortisol response. In this study we investigate the relative impact of exposure to childhood maltreatment and concurrent depression on adulthood cortisol levels. Methods: The sample comprised 103 offspring from the South London Child Development Study (SLCDS), a prospective longitudinal birth cohort study set up in 1986 that has followed mothers and their offspring from pregnancy to 25 years. Data on offspring exposure to childhood maltreatment (birth to 17 years), offspring adulthood depression and offspring adulthood cortisol levels was obtained through one-to-one clinical interview. Results: There was a significant main effect for cortisol levels at 30 minutes post-awakening, F[3, 65] = 3.4, p = .021. Post hoc analyses revealed that adults exposed to childhood maltreatment but who were not depressed in adulthood had significantly higher 30-minute cortisol (mean difference = 4.2, SE = 1.5, p = .024) compared to those who were non-depressed and non-maltreated, and in comparison to those maltreated and also depressed (mean difference = 5.0, SE = 1.7, p = .021). These data suggest hyperactivity in the cortisol response system amongst maltreated (but not depressed) offspring, and that the experience of depression in conjunction with childhood maltreatment leads to blunting of the cortisol awakening response. Conclusions: These findings demonstrate that exposure to childhood maltreatment has effects on the HPA axis that persist into young adulthood which are modulated by the presence of depressive psychopathology. Financial Support: Psychiatry Research Trust, MRC UK
MC19

IMPAIRED FACE EMOTION RECOGNITION IN DEPRESSION: THE INFLUENCE OF PHARMACOLOGICAL AND PSYCHOLOGICAL FACTORS

Anderson IM, Neuroscience and Psychiatry Unit, Inst of Brain, Behaviour and Mental Health, Stopford Bldg, Univ of Manchester, Oxford Rd, Manchester, M13 9PT, kate.williams-4@manchester.ac.uk

Recognition of different emotions is important for social cognition. We previously reported generally impaired face emotion recognition in major depression (Anderson et al., 2011, BJPsychiatry, 198, 302-308). It has also been reported that acute citalopram selectively increases recognition of fearful faces (Harmer et al., 2003, Neuropsychopharmacology, 28, 148-152). In this study we attempted to replicate our previous findings and to investigate the effect of an acute citalopram infusion on face emotion recognition in healthy and depressed participants. 32 unmedicated depressed, and 25 healthy participants, age and sex matched, received a face emotion recognition task (Anderson et al 2011) at baseline and a few days later following citalopram 7.5mg IV or saline (random double-blind allocation). The analysis was limited to happy, sad and fearful emotions; participants were assessed for depression (MADRS), rumination (Ruminative Response Scale, RRS) and childhood trauma (Childhood Trauma Questionnaire, CTQ). Analysis was by repeated measures ANOVA (emotion and time within subject, group and drug between subjects). Linear regression was used to explore predictors of emotion recognition accuracy in all subjects. Depressed participants identified all three emotions less accurately than controls (group: F (1, 53) = 5.40, p=0.024) with happy recognised more accurately than sad and fear (emotion: F (2, 106) = 87.06, p<0.001). No effects of time, drug administration or interactions were found. In controls RRS-depression and CTQ scores correlated negatively with happy face recognition (r=-0.37, p=0.045 and r=-0.49, p=0.006 respectively); in depressed participants CTQ score correlated negatively with sad face recognition (r= -0.36, p=0.04). Linear regression analysis: happy recognition was predicted by RRS score (R2=0.10, F (1,60) = 6.44, p=0.014) whereas sad recognition was predicted by CTQ score (R2=0.12, F (1,60) = 7.84, p=0.007). We replicated our previous finding of impaired face emotion recognition irrespective of valence but were not able to show acute effects of citalopram on fear recognition; low citalopram dose or task differences may explain this. One interpretation of the linear regression analysis is that happy recognition accuracy may relate to the depressive state with sad recognition accuracy more strongly influenced by childhood trauma; however group correlational analysis also suggests a possible effect of childhood trauma on happy recognition in healthy individuals. These results add further weight to the importance of childhood trauma on the processing of emotions in adulthood. Supported by a grant from the MRC.

MC20

EARLY EFFECTS OF DULOXETINE ON EMOTION RECOGNITION IN HEALTHY VOLUNTEERS

Bamford S, School of Psychology, Univ of Southampton, College Keep 4-12 Terminus Terrace Southamptom, SO14 3DT, s.bamford@soton.ac.uk

Introduction: The serotonin-noradrenaline reuptake inhibitor (SNRI) duloxetine is an effective treatment for major depression and generalized anxiety disorder. Neuropsychological models of antidepressant drug action suggest therapeutic effects might be mediated by the early correction of maladaptive biases in emotion processing, such as emotional expression recognition. Sub-chronic administration of duloxetine (for two weeks) produces adaptive changes in neural circuitry implicated in emotion processing; however, its effects on emotional expression recognition have not been examined. Method: Forty healthy participants were randomized to receive either 14 days of duloxetine (60mg/day, titrated from 30mg after 3 days) or matched pill placebo (with sham titration) in a double-blind, between-groups, repeated measures design. On day 0 and day 14 participants completed a computerized emotional expression recognition task that measured sensitivity to the six primary emotions; sadness, happiness, anger, fear, disgust and surprise. Results: Duloxetine, compared to placebo, selectively reduced the recognition of sadness. Analysis of Hits and False Alarms provided no evidence that duloxetine altered the recognition or incorrect classification of other emotions. The effect of duloxetine on emotion recognition occurred in the absence of changes in reported mood. Conclusions: The effect of sub-chronic duloxetine administration on the recognition of sadness indicates a mechanism through which SNRIs may target negative biases in emotion processing to achieve therapeutic effects. Our findings complement evidence that maladaptive processing of sadness may be a therapeutic target in major depression, and that sub-chronic administration of other classes of antidepressant can reduce the recognition of negative emotion in healthy individuals. This research was funded by MRC grant MR/J011754/ awarded to M.G, D.S.B and M.R.M and which employs S.B. V.P is funded by an ESRC PhD-studentship. MRM is a member of the UK Centre for Tobacco and Alcohol Studies, a UKCRC Public Health Research: Centre of Excellence. Funding from British Heart Foundation, Cancer Research UK, Economic and Social Research Council, Medical Research Council, and the National Institute for Health Research, under the auspices of the UK Clinical Research Collaboration, is gratefully acknowledged.
MC21

QUETIAPIN MODULATES GLOBUS PALLIDUM INTERNUM DURING THE ANTICIPATION OF NEGATIVE AND POTENTIALLY NEGATIVE EMOTIONAL STIMULI

Bruhl AB, BCNI and Dept of Psychiatry, Univ of Cambridge, Downing site Cambridge, CB2 3EB, abb41@medschl.cam.ac.uk
Scherpier S (2), Opialla S (2), Weidt S (3), Jäncke L (4), Herwig U (2) (1) Behavioural and Clinical Neuroscience Inst and Dept of Psychiatry, Univ of Cambridge (2) Clinic for Psychiatry, Psychotherapy and Psychosomatics, Univ Hospital of Psychiatry Zurich, Zurich (3) Dept of Psychiatry and Psychotherapy, Univ Hospital Zurich, Zurich (4) Dept of Psychology, Division Neuropsychology, Univ of Zurich, Zurich

Background: The anticipation and perception of emotional stimuli is a model activating emotion processing circuits in depression and anxiety disorders. Until now, the exact way how psychopharmacological agents such as antidepressants modulate the neural circuits involved in emotion processing is only partially known. Besides serotonergic and noradrenergic pathways, dopaminergic mechanisms have come into the focus of antidepressant treatment. This study aimed at identifying brain regions modulated by quetiapine, which is a dopamine receptor antagonist (D1, D2), besides an antagonistic effect at the 5-HT1A-receptor. Methods: We conducted a single-blind pseudo-randomized crossover pharma-co-fMRI study. Brain activation after ingestion of a single dose of the dopaminergic antagonist quetiapine (100 mg) is compared to placebo during the cued anticipation of emotional stimuli in 21 healthy participants. The emotional anticipation task comprised the cued anticipation and subsequent perception of emotional pictures of either ‘known’ emotional valence (positive, negative, neutral) or ‘unknown’ valence, that could have been positive or negative. The fMRI data were analysed with two repeated-measures ANOVA on the interaction between the task condition (anticipation negative, unknown, positive versus neutral; perception negative and positive versus neutral) and the treatment condition (quetiapine, placebo). The statistical threshold was set at p < 0.0005 with a cluster extend threshold of 135 mm3 (5 voxel à 3x3x3 mm). Results: The dopamine antagonist quetiapine increased activity compared to placebo in the left ventral striatum during the anticipation of negative and unknown announced stimuli. There was no significant difference in the perception of negative stimuli comparing quetiapine and placebo during the anticipation of positive versus neutral stimuli. At the chosen statistical level of p < 0.0005, we found no significant results when comparing quetiapine and placebo during the perception of negative and positive versus neutral pictures. At the lower exploratory level of p < 0.005 (cluster extend threshold 135 mm3), the interaction analysis of the perception condition resulted in two clusters in the right middle temporal gyrus, where quetiapine dampened activity during the perception of negative stimuli compared to placebo. Discussion: The main effect of acute blockade of D1 and D2 dopaminergic receptors by quetiapine seems to be an increased activation of the Globus pallidum internum during the anticipation of negative and possibly negative stimuli. The effects of quetiapine during the perception of emotional stimuli were much weaker. The effect of dopaminergic modulation of the basal ganglia could be a correlate of changed reward processing due to quetiapine treatment. Supported by Swiss National Fonds 112 631.

MC22

INVESTIGATING POSITIVE AND NEGATIVE INFORMATION PROCESSING AS TRAIT MARKERS FOR DEPRESSION

Frey AL, Psychology Dept, Univ of Reading, School of Psychology and Clinical Language Sciences, Whiteknights, Reading, UK, RG6 6AL, anna-lena.frey@hotmail.com
Malinowska L(1), McCabe C(2) (1), (2) Psychology Dept, Univ of Reading, Reading RG6 6AL

Background: A better understanding of the aetiology of major depressive disorder (MDD) will guide treatment development. This may be achieved by finding trait markers, which are behavioural or biological abnormalities that are present before illness onset in people who are at risk of the disorder. Decreased processing of rewarding information (anhedonia) and increased processing of negative information (negative bias) are thought to be possible trait markers for MDD (Hasler et al. 2004, Neuropsychopharmacology, 29, 1765–1781). However, it is unknown which of the reward processing subtypes (wanting and liking) are trait markers for depression. Preclinical research on dopamine function suggests that diminished wanting is a trait marker for MDD while decreased liking is not (Cannon & Palmiter, 2003, The Journal of Neuroscience, 23, 10827-10831; Cousins et al., 1996, Behavioural Brain Research, 74, 189-197). The current study aimed to examine the behavioural response to negative and positive (wanting and liking) information in young people who are at risk of MDD by virtue of having a parent with depression. Methods: We examined 23 individuals with a family history of depression (FH+) and 21 controls on tasks involving rating the liking of positive, neutral and negative food pictures and measuring the wanting of a chocolate reward in an effortful key pressing task. Results: An equivalence test confirmed the hypothesis that there were no group differences in the liking ratings of positive food pictures, as the lower (-6.92%) and upper (5.54%) bound of the 95% confidence interval of the mean difference of ratings fell within the zone of scientific indifference (of +/- 11%). Furthermore, an independent samples t-test indicated that there were no differences in the wanting task performance between groups (p = 0.578). However, a Mann-Whitney U test revealed that FH+ participants’ ratings of negative food pictures were significantly lower than HC participants’ ratings (p = 0.015). Conclusions: Our findings show that negative stimuli were rated as more negative by FH+ individuals than by controls, which is in line with the notion of a negative bias as a trait marker for MDD. As only approximately 40% of young people with a parent with depression go on to have MDD themselves (Beardslee et al., 1998, Journal of the American Academy of Child and Adolescent Psychiatry, 37,1134 –1141), future longitudinal studies with larger group samples are needed to determine if decreased wanting of positive stimuli might be a valid trait marker for MDD. Source of financial sponsorship: Dr McCabe Start-Up Funds University of Reading.
MC23

DEFICITS IN SOCIAL REWARD PROCESSING BEHAVIOUR IN THOSE AT RISK OF DEPRESSION COMPARED TO HEALTHY CONTROLS

Iqbal S, School of Psychology and Clinical Language Science, Univ of Reading, Psychology Dept, Earley Gate, Whiteknights Rd, RG6 7BE, sosomya.i@gmail.com
Sharma S(1) McCabe C(1) (1) Psychology Dept, Univ of Reading, Reading, UK. Earley Gate, Whiteknights Rd. RG6 7BE

Background: Depression features social withdrawal and lack of pleasure and motivation for social experiences this is known as anhedonia (Ribot 1897, The psychology of emotions). Those recovered from depression and those at increased risk of depression have deficits in neural responses to positive and negative stimuli, indicating possible trait markers (McCabe et al. 2009, Psychopharmacology, 205: 667-77; McCabe et al. 2012, Biol Psychiatry, 72(7), 588-594). However, how social reward processing might be a specific risk factor for depression has yet to be elucidated. We investigated response to social reward in a never depressed, at risk group, those with a familial history of depression (FH+) compared to healthy controls. Methods: We recruited 44 females, 24 FH+ and 20 controls. We designed a novel social reward task utilising smiles. The task involved responding to 2 faces on a screen that had genuine, polite or neutral smiles. We had 3 conditions (1: genuine vs polite; 2: neutral vs polite; 3: neutral vs genuine). In an implicit phase of the task subjects were asked which of the 2 smiles on the screen they preferred and in an explicit phase they were asked which smile was the genuine smile. We measured both preference and reaction time data. Results: Using independent sample t-tests we found a significantly increased preference in the FH+ group compared to the control group for the polite smile over the neutral smile (p=0.016) and a faster reaction time in the FH+ group compared to the control group when choosing the polite vs the neutral smile (p=0.02). Conclusion: Our results indicate that there are differences in the behavioural responses to social cues such as smiles in those at risk of depression. The FH+ group thought the polite smiles more genuine than the control group and were quicker in their judgment of this than the control group. This is interesting in that the polite vs the neutral condition was the most ambiguous condition in our task, in that there were no genuine smiles. Therefore it is possible that our results indicate that those at risk of depression have deficits in social decision making but only under more ambiguous situations. Future studies with larger sample sizes are needed to understand how differences in social reward might be trait markers for disorders such as depression. This kind of research could aid the detection of early signs of risk for depression and help guide prevention strategies.

MC24

LSD ENHANCES EMOTIONAL RESPONSES TO MUSIC: IMPLICATIONS FOR PSYCHEDELIC-ASSISTED PSYCHOTHERAPY?

Kaelen M, Centre for Neuropsychopharmacology, Div of Brain Sciences, Fac of Medicine, Imperial College London, Burlington Danes Bldg, Hammersmith Campus, 160 Du Cane Rd, London, W12 ONN, m.kaelen@imperial.ac.uk
Barrett FS (2) Roseman L (1) Bolstridge M (1) Feilding A (3) Nutt DJ (1) Carhart-Harris RL (1) 2 Dept of Psychiatry and Behavioral Sciences, Johns Hopkins Univ School of Medicine 3 The Beckley Foundation, Beckley Park, Oxford, UK

Lysergic acid diethylamide (LSD) is a classic psychedelic drug and non-selective serotonin 2A agonist that has a history of use as a tool to assist psychotherapy for the treatment of mood disorders and addiction. Modern trials are currently underway to explore LSD’s therapeutic value, and consistent with the historical work, the treatment sessions incorporate music listening as a putative therapeutic aid. It is hypothesised that LSD enhances emotional responses to music and this can improve therapeutic outcomes, although these assumptions have never been empirically tested. The aim of the present study was to test these hypotheses in a single blind, placebo-controlled design with healthy volunteers. Ten volunteers (1 female, mean age = 34.2 ± 7.3) received intravenous LSD (40-80 µg) and placebo (saline) on two separate occasions in a comfortable, clinical environment. Ten music tracks of the neo-classical and ambient genre were selected from an original sample of 18 and were chosen based on a pre-study analysis of their emotional “potency”. The 10 selected tracks were split into two versions of five and balanced for duration and potency based on the pre-study data. The order in which these versions were presented was counterbalanced across conditions. On each visit, volunteers listened to five different tracks at 5 specific time points (45-240 minutes) post-infusion. Volunteers rated their emotional response to the music immediately after the end of each track using validated assessment tools (i.e. Visual Analogue Scale ratings and the Geneva Emotional Music Scale, GEMS-9, which rates 9 different emotional responses typical to music listening). Volunteers rated being significantly more emotionally affected by music under LSD than placebo (mean for LSD = 0.71, SD=0.14, mean for placebo = 0.51, SD=0.17; p = 0.006 (2-tail), t = -3.56 , df = 9) and 2-tailed t-tests for GEMS-9 ratings showed that LSD specifically enhanced the dimensions; “transcendence” (p=0.009), “wonder” (p = 0.01), “power” (p=0.01), “tenderness” (p=0.02) and “tension” (p=0.04) but not “sadness” (p=0.36), “nostalgia” (p=0.18), “peacefulness” (p=0.20) or “joyfulness” (p=0.14). Ratings of drug intensity correlated positively with ratings of transcendence (2-tail, p = 0.008 , r =0.61). These results support the inference that LSD enhances emotional responses to music and highlight specific aspects of emotion that appear to be most sensitive to this enhancement. Future research will assess whether the effects demonstrated here in healthy volunteers have therapeutic relevance in a clinical sample. Financial support was provided by the Beckley Foundation.
**MC25**

**AGEING, EMOTION, AND DEPRESSION: THE IMPACT OF A HISTORY OF MAJOR DEPRESSIVE EPISODES ON AFFECTIVE COGNITION IN THE ELDERLY**

McFarquhar M, Neuroscience & Psychiatry Unit, The Univ of Manchester, G.803 Stopford Bldg Oxford Rd Manchester, M13 9PL, martyn.mcfarquhar@postgrad.manchester.ac.uk

Trotter PD(1), Thomas E(2), Sahakian B(3), Deakin JFW(2), Anderson IM(2), Juhasz G(2,4), Elliott R(2) (1) Liverpool JMU, Natural Sciences and Psychology, Tom Reilly Bldg, Byrom St, Liverpool, L3 3AF (2) NPU, School of Community Based Medicine, Faculty of Medical and Human Sciences, Manchester, M13 9PL (3) Dept of Psychiatry, School of Clinical Medicine, Addenbrooke’s Hospital, Cambridge, CB2 2QQ (4) Dept of Pharmacodynamics, Faculty of Pharmacy, Semmelweis Univ, Budapest

Introduction: Both the affective and non-affective cognitive profiles of currently depressed individuals have been well investigated. Increasing evidence suggests that differences in affective cognition, as seen in currently depressed individuals compared with healthy controls, can also be seen in remitted depressed (rMDD) individuals, representing a bias towards processing negative information. Research into normal ageing suggests the development of a bias towards processing positive information as individuals age. At present it is unknown what influence previous depression has in remitted depressed (rMDD) individuals, representing a bias towards processing negative information. Research into normal ageing suggests the development of this bias. The aim of the present study was to investigate the interaction between normal ageing and rMDD using a battery of affective neurocognitive tasks. Methods: We recruited 39 older and 39 younger participants with rMDD, and 39 older and 39 younger never-depressed controls. We administered tasks designed to investigate emotional attention, emotional memory, emotional categorisation, and social emotions. Data were analysed using linear and generalized linear mixed-effects models. Results: Evidence of the positivity effect of ageing was found in all domains. Clear evidence of biased categorisation of sad faces was found in rMDD. An interaction between the positivity effect and negative bias was found in the emotional faces, attention, and social emotions tasks. No interaction was found for the emotional memory task. Conclusions: Our findings do not suggest that a history of depression inhibits the positivity effect of ageing. It appears that a history of depression confers an additional negativity bias in old age. The never-depressed older adults therefore exhibited biases towards positive stimuli and away from negative stimuli, whereas the rMDD older adults showed a bias towards both positive and negative stimuli. This difference is explained by appealing to the concept of an emotionally gratifying processing bias compared with an emotionally relevant processing bias. Funding: The research was funded by a grant from the MRC (ref: G0900593), M. McFarquhar was supported by an MRC Studentship.

**MC26**

**EXAGGERATED LOSS-SPECIFIC PAVLOVIAN-INSTRUMENTAL TRANSFER IN UNMEDICATED MAJOR DEPRESSION**

Nord CL, Inst of Cognitive Neuroscience, UCL, 17 Queen Square, London, WC1N 3AR, camilla.nord.11@ucl.ac.uk

Lawson RP(1)(2), Huys Q(3), Roiser JP(1) (1) Inst of Cognitive Neuroscience, UCL, 17 Queen Square, London, WC1N 3AR (2) Wellcome Trust Centre for Neuroimaging, UCL, 12 Queen Square, London, WC1N 3BG (3) Translational Neuromodeling Unit, ETH and Univ of Zürich, Wilfriedstrasse 6, 8032 Zürich, Switzerland

Introduction: Cues drive both adaptive goal-directed behaviour, such as seeking out food or water, and maladaptive behaviour, such as drug-seeking. The influence of cues on behaviours can be explored through Pavlovian-to-instrumental transfer (PIT), which examines the relation between passively-conditioned Pavlovian cues and an instrumental conditioning task. We investigated PIT in patients with major depression (MDD). Given the negative affective biases present in depression, we predicted that depressed patients would show an enhanced PIT effect, specific to negatively-valenced stimuli. Methods: We administered a computerised PIT task to 28 healthy controls and 25 unmedicated patients with MDD. The task was made up of two blocks separately examining approach and withdrawal instrumental responses (go- or no-go, respectively). Each block comprised three stages: an instrumental training stage, where subjects learned the probabilistic values of twelve stimuli instrumentally associated with monetary gain and loss, a Pavlovian training stage, where five fractal images were each paired with a monetary value (+£1, +£0.1, +0, -£0.1, and -£1), and a combined stage, where both types of stimuli were displayed simultaneously to measure PIT, or the influence of the background (Pavlovian) stimulus on the foreground (instrumental) responses. Results: A repeated-measures ANOVA revealed a significant three-way interaction between patient status, Pavlovian stimulus valence, and type of block (approach or avoidance), F(4,208) = 5.396, p<0.01. The PIT effect was also observed for all participants, with a significant interaction between stimulus valence and type of block F(4,208) = 11.609, p<0.001. Linear contrasts revealed significant differences between patients and controls in the withdrawal condition for both categories of negatively-valenced Pavlovian stimuli: those associated with a moderate punishment t(52) = -2.4, p<0.05, and those associated with a large punishment t(52) = -2.732, p<0.01, with depressed patients showing an enhanced PIT effect. Conclusions: We observed an exaggerated PIT effect in depressed patients in the presence of negatively-valenced Pavlovian stimuli. That is, when the instrumental task was performed in conjunction with background images previously associated with both small and large monetary losses, depressed patients were less able to overcome the Pavlovian bias toward withdrawal. These results demonstrate an enhanced influence of automatic associations, specific to negative stimuli, in depression. This finding sheds light on the cognitive mechanisms of major depression, and paves the way for future studies to explore overcoming these negative Pavlovian biases in the treatment of depression. Research funded by the Medical Research Council.
MC27
SCREENING FOR DEPRESSION RESILIENCE: THE IMPACT OF A TRANSLATIONAL STRESS-TEST ON DECISION MAKING IN HEALTHY HUMANS
Robinson OJ, ICN UCL, 17 Queen Square, London, WC1N 3AR, o.robinson@ucl.ac.uk
Bond R(1), Roiser JP(1) (1)ICN, UCL, 17 Queen Square, London

Stress can profoundly alter cognitive function. How an individual responds to stress is, moreover, critical for resilience to mood and anxiety disorders. Despite this, surprisingly little is known about the impact of stress on decision-making processes, or how this may relate to psychiatric disorder susceptibility. This study therefore examined the impact of a translational stress paradigm (threat of unpredictable shock) in a sample demonstrating a naturalistic range of current depressive symptoms on two well established decision-making paradigms. We predicted that stress would promote harm-avoidant decision-making, especially in those most resilient to depressive symptoms. Healthy participants (N=49) completed a forced choice version of the Iowa gambling task (IGT) and a decision-making task designed to elicit framing effects (i.e. increased risk-taking in the context of losses). Each task contained alternating threat (risk of infrequent and unpredictable electrical shocks) and safe conditions. In accordance with contemporary approaches to psychiatry, a relaxed screening procedure was utilized to capture a wide a range of Beck depression inventory (BDI) scores. Subjects were divided according to BDI into 3 groups of no (N=15;BDI=0-2), low (N=16;BDI=3-7) and moderate depression (N=17;BDI=8-26) symptoms. Self-report revealed that threat of shock reliably increased anxiety in all subjects (F=140,p<0.001). Significant framing effects were seen (F=50,p<0.001) but these were insensitive to stress (p=0.4) and depression symptoms (p=0.6). On the IGT subjects learned to avoid the bad decks (F=49,p<0.011) but this was sensitive to both stress and depression symptoms. Specifically subjects with no current depressive symptoms demonstrated stress-potentiated harm-avoidance; i.e they rejected more disadvantageous decks under threat than safe; a pattern that was not present in low and moderate symptom groups (threat*deck-type*group: F=3.4,p=0.04/BDI as a continuous variable: F=4.7,p=0.04) Individuals with no self-reported depression symptoms therefore demonstrate a putatively adaptive response to stress that is not present in those with low to moderate symptoms. Specifically, stress promotes harm avoidant behaviour in this group as evidenced by reduced selection of disadvantageous decks under threat of shock. This may be a marker of resilience in healthy individuals free from depressive symptomatology. Going forward the goal will be to develop interventions which promote such putative markers of resilience in healthy individuals Funding: MRC Career Development award to Oliver Robinson

MC28
EARLY CHANGES IN NEURAL RESPONSE TO EMOTIONAL STIMULI PREDICT CLINICAL RESPONSE TO SSRI TREATMENT IN DEPRESSION
Godlewksa BR, Dept of Psychiatry, Univ of Oxford, Warneford Lane Oxford, OX3 7JX, beata.godlewksa@psych.ox.ac.uk
Browning M(1), Norbury R(1), Cowen PJ(1), Harmer CJ(1) Univ Dept of Psychiatry, Warneford Hospital, Oxford, OX3 7JX

Introduction: Antidepressant treatment has been shown to modulate behavioural and neural markers of negative affective bias in depressed patients. These effects can be measured early in treatment and may be key mechanisms of later clinical improvement. If this account is correct, early changes in emotional bias should be predictive of later clinical changes in depression. Methods: In the current study, 35 unmedicated patients meeting DSMIV criteria for major depression were prescribed the SSRI escitalopram (10mg) over 6 weeks. The neural response to fearful and happy emotional facial expressions was assessed both before and after 7 days of treatment. FMRI data was acquired at a 3T scanner. Results: Early changes in the neural response to fearful vs happy facial cues were compared between those patients who were classified as responders vs non-responders by week 6. Twenty-two (65%) patients responded to escitalopram by the end of treatment. This group had a greater reduction in neural response to fearful vs happy facial expressions after 7 days of escitalopram compared to non-responders across a network of regions including the anterior cingulate, insula, and thalamus (P<0.05, FEW corrected whole brain analysis), with a cluster in the amygdala using small volume correction. This prediction was seen over and above baseline severity ratings in depression and anxiety and early change in depression ratings at day 7. Responders and non-responders did not differ in terms of age, gender, duration of the current episode or baseline depression scores. Conclusions: These results support the hypothesis that early changes in the neural processing of emotional information with SSRI treatment are important for later clinical improvement, following environmental exposure and learning in the context of a reduced negative bias, and that they do not depend on concurrent mood change. As such, early correction of negative bias may be a key mechanism of antidepressant drug action and may provide an early neural biomarker of clinical response to antidepressant treatment in depression. This study was funded by Medical Research Council.
MD01

FIBRILLARY ASTROCYTES ARE DECREASED IN THE SUBGENUAL CINGULATE IN SCHIZOPHRENIA

Williams MR, MRC Imaging Unit, Centre for Clinical Sciences, Mansfield Bldg, Hammersmith Hospital, Du Cane Rd, London, W12 0NN, matthew.r.williams@imperial.ac.uk
Pearce RKB (1), Hirsch SR (1), Maier M (2) (1) Neuropathology Unit, Lab Block, Charing Cross Hosp, St. Dunstans Rd, London, W6 8RF (2) Trust HQ, St. Bernards Hosp, Uxbridge Rd, UB1 3EU

Abstract fibrillary acid protein (GFAP) mRNA in the anterior cingulate cortex have been reported changed in mood and affective disorders. Our study examines the relative density and frequency of fibrillary and gemistocytic astrocytes in the white matter of the subgenual cingulate cortex in 11 schizophrenia, 16 bipolar disorder, 20 major depression and 20 normal control cases. Serial coronal sections were stained with H&E for anatomical guidance and GFAP immunohistochemistry for astrocyte identification. Astrocyte density was measured using systematic anatomical distinctions and randomised counting methods previously reported. Astrocytes were classified as fibrillary, commonly known as reactive, or gemistocytic based on staining and morphometric criteria and were measured in the crown and base of the gyral white matter. Fibrillary astrocytes were decreased in the base of the cingulate white matter in schizophrenia (p = 0.046), with no change in the density of gemistocytic astrocytes. There was no change in density of gemistocytic astrocytes. This suggests that the previously reported decrease in astrocyte density and in glial astrocytes in schizophrenia in the subgenual cingulate is accounted for only by a change in fibrillary astrocytes. As cultured astrocytes have shown a change in GLT-1 and GLAST expression dependent on morphological type this finding gives a possible mechanism for the glutamate disregulation underlying psychosis. No funding received for this study.

MD02

MIDBRAIN DOPAMINE DYSFUNCTION AND SYMPTOMS IN SCHIZOPHRENIA- A POST-MORTEM AND PET IMAGING STUDY

Williams MR, MRC Imaging Unit, Centre for Clinical Sciences, Mansfield Bldg, Hammersmith Hospital, Du Cane Rd, London, W12 0NN, matthew.r.williams@imperial.ac.uk
Pearce RKB (1) Hirsch SR (1) Maier M (2) Turkheimer F (3) & Howes O (4) (1) Neuropathology Unit, Lab Block, Charing Cross Hosp, St. Dunstans Rd, London, W6 8RF (2) Trust HQ, St. Bernards Hosp, Uxbridge Rd, London, UB1 3EU (3) Inst of Psychiatry, King’s College London, 16 De Crescigny Park, London, SE5 8AF (4) MRC Imaging Unit, Mansfield Bldg, Hammersmith Hospital, Du Cane Rd, London, W12 0NN

Elevated in vivo markers of presynaptic striatal dopamine activity have been a consistent finding in schizophrenia, and include a large effect size elevation in dopamine synthesis capacity. However, it is not known if the dopaminergic dysfunction is limited to the striatal terminals of dopamine neurons, or is also evident in the dopamine neuron cell bodies, which mostly originate in the substantia nigra. The aim of our studies was therefore to determine whether dopamine synthesis capacity is altered in the substantia nigra of people with schizophrenia, and how this relates to symptoms. In a post-mortem study, a semi-quantitative analysis of tyrosine hydroxylase staining was conducted in nigral dopaminergic cells from post-mortem tissue from patients with schizophrenia (n = 12), major depressive disorder (n = 13) and matched control subjects (n = 13). In an in vivo imaging study, nigral and striatal dopaminergic function was measured in patients with schizophrenia (n = 29) and matched healthy control subjects (n = 29) using 18F-dihydroxyphenyl-L-alanine (18F-DOPA) positron emission tomography. In the post-mortem study we found that tyrosine hydroxylase staining was significantly increased in nigral dopaminergic neurons in schizophrenia compared with both control subjects (P 5 0.001) and major depressive disorder (P 5 0.001). There was no significant difference in tyrosine hydroxylase staining between control subjects and patients with major depressive disorder, indicating that the elevation in schizophrenia is not a non-specific indicator of psychiatric illness. Larger scale examination of post-mortem nigra showed astrocyte density was decreased in schizophrenia compared to controls (p = 0.030), with no change in oligodendrocyte density. Significantly increased nuclear cross- sectional area (p = 0.017) and length (p = 0.021), and increased nucleolar volume (p = 0.037) in dopaminergic neurons were observed in schizophrenia patients compared with controls, suggesting nuclear pleomorphic changes. No changes were observed in depression cases compared to control group. In the in vivo imaging study we found that 18F-dihydroxy-phenyl-L-alanine uptake was elevated in both the substantia nigra and in the striatum of patients with schizophrenia (effect sizes = 0.85, P = 0.003 and 1.14, P 5 0.0001, respectively) and, in the voxel-based analysis, was elevated in the right nigra (P 5 0.05 corrected for family wise-error). Furthermore, nigral 18F-dihydroxyphenyl-L-alanine uptake was positively related with the severity of symptoms (r = 0.39, P = 0.035) in patients. However, whereas nigral and striatal 18F-dihydroxyphenyl-L-alanine uptake were positively related in control subjects (r = 0.63, P 5 0.001), this was not the case in patients (r = 0.30, P = 0.11). These findings indicate that elevated dopamine synthesis capacity is seen in the nigral origin of dopamine neurons as well as their striatal terminals in schizophrenia, and is linked to symptom severity in patients. This work was funded by a Medical Research Council (UK) grant to Dr Howes (grant number: MC-A656-5QD30) and the National Institute of Health Research Biomedical Research Council grant to King’s College London.
MD03

EVIDENCE FOR NEUROINFLAMMATION IN MAJOR DEPRESSIVE DISORDER AND IN SCHIZOPHRENIA – A POSITRON EMISSION TOMOGRAPHY (PET) STUDY USING 11C-(R)-PK11195

Holmes SE, Wolfson Molecular Imaging Centre, Univ of Manchester, 27 Palatine Rd Manchester, M20 3LJ, sophie.holmes@manchester.ac.uk

There is considerable interest in whether major depressive disorder (MDD) and schizophrenia are associated with neuroinflammation. Microglial activation, a measure of neuroinflammation, can be quantified using PET ligands specific for the 18kDa translocator protein (TSPO) which is overexpressed by activated microglia. A recent PET study found no evidence for increased TSPO levels in mild-to-moderate MDD (Hannestad et al, 2013. Brain Behav Immun. 33:131-8), while initial PET studies in schizophrenia have shown evidence for increased TSPO. However, these initial studies might be confounded by low numbers, mild severity and antidepressant/antipsychotic medication. We present an interim analysis of an ongoing study investigating neuroinflammation in mostly medication-free, moderate-to-severe MDD and schizophrenia. Seven individuals (4 males; mean±SD age: 27±12.8) in a DSM-IV major depressive episode (MDE) of at least moderate severity (mean BDI 30±4.5), eight patients (5 males; mean±SD age 32±8.4 yr) with a diagnosis of DSM-IV schizophrenia of at least moderate severity (mean PANSS score 84±10.5) and 8 age- and gender-matched healthy controls (5 males; age 31±10.5 yr) underwent a 60 minute dynamic PET scan with 11C-(R)-PK11195 using the High Resolution Research Tomograph. A grey matter cerebellum input function was used to generate parametric maps of BPND using the simplified reference tissue method. All MDE patients were antidepressant-free and 6 of the 8 schizophrenia patients were antipsychotic-free for at least 3 months prior to scanning. Globally, mean BPND was higher in depression patients (0.12±0.06) and in schizophrenia patients (0.10±0.05) compared to controls (0.07±0.04). Univariate ANOVAs revealed significant main effects of group in both depression (F (1, 8) = 33.01, p<0.001) and in schizophrenia (F (1, 8) = 8.60, p=0.004) across all 9 ROIs. Post hoc analysis on the depression data showed significantly higher TSPO binding in frontal cortex, insula (p<0.05), anterior cingulate cortex, posterior cingulate cortex and thalamus (p<0.001) (unpaired t-tests). In the schizophrenia patients, there was significantly higher TSPO binding in ACC (p<0.05) with binding in frontal cortex reaching trend significance (p=0.08). This interim analysis provides evidence of neuroinflammation in moderate-to-severe medication-free depression and in a cohort of mostly drug-free schizophrenic patients. The full cohorts (n=16 in each) need to be recruited for confirmation and further interpretation of results. If neuroinflammation is confirmed in either disorder, there will be important implications for future treatment strategies. This study is part-funded by the University of Manchester, the Engineering and Physical Sciences Research Council and the British Medical Association.

MD04

RESTING CEREBRAL BLOOD FLOW (RCBF) AND PERIPHERAL BIOMARKERS OF INFLAMMATION AND NEUROGENESIS IN FIRST EPISODE PSYCHOSIS

Giordano AG, Dept of Psychosis Studies, Inst of Psychiatry, 16 De Crespigny Park London, SE5 8AF, annalisa.giordano@kcl.ac.uk

Introduction: Peripheral markers of inflammation and neurogenesis factors are altered in psychosis, but it remains unclear whether these are associated with alterations in regional Cerebral Blood Flow (rCBF). This study investigated weather C-Reactive Protein (CRP) and Vascular Endothelial Growth Factor (VEGF) serum levels influence cerebral rCBF in patients with first episode psychosis and healthy individuals.

Methods: In 13 patients and 14 healthy controls, matched for age and gender, we evaluated blood levels of CRP and VEGF. We estimated rCBF using a pseudo-continuous arterial spin labelling (pCASL) sequence. We compared peripheral biomarkers and rCBF between the two groups, and evaluated whether peripheral markers were correlated with rCBF. Results: Compared to controls, patients had higher CRP (1.8±2.3 vs. 0.5±0.1 respectively, p=0.07) and higher VEGF (66.7±18.5 vs. 58.7±36.9 respectively, p=0.04) levels. Patients also showed higher rCBF in superior frontal and postcentral gyri, and lower rCBF in the parahippocampal gyrus (all p<0.001, uncorrected). Moreover, higher rCBF in the hypothalamus was significantly associated with lower CRP, and higher rCBF in the cingulate gyrus with lower VEGF (all p<0.05, FWD corrected). Conclusions: These findings go beyond previous evidence that peripheral inflammatory markers are raised in psychosis and reveal increased VEGF peripheral levels. Furthermore, the study shows both biomarkers may be associated with changes in perfusion in brain areas which have been found implicated in schizophrenia. Further work will need to clarify the role of the CRP and VEGF in modulating rCBF and their relationship with antipsychotic treatment and symptom severity. Acknowledgements The research was in part financially supported by the National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London.
MD05

THE EFFECT OF CHILDHOOD TRAUMA ON THE HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXI S ACTIVITY IN FIRST EPISODE PSYCHOSIS

Tomassi S, Dept of Public Health and Community Medicine, Section of Psychiatry, Univ of Verona and Azienda Ospedaliera Univ Integrata Verona, Piazzale L.A. Scuro 10, Verona, Italy, 37134, simona.tomassi@kcl.ac.uk

Brondino N (2), Faravelli C (3), Mondelli V (4), Bonetto C (1), Ira E (1), Politi P (2), Fioravanti G (3), Lasalvia A (1), Santonastaso P (5), Torresani S (6), Miceli M (7), Neri G (8), Pileggi F (9), Ghigi D (10), Scarone S (11), Cocchi A (12), Brambilla P (13), Ruggeri M (1), Tosato S (1), Pariante C (4) and the GET-UP Group (1) Dept of Public Health and Community Medicine, Section of Psychiatry, Univ of Verona, and Azienda Ospedaliera Univ Integrata Verona, Verona, Italy (2) Section of Psychiatry, Univ of Pavia, Pavia, Italy (3) Dept of Psychology, Univ of Florence, Florence, Italy (4) Inst of Mental Health, Azienda ULSS, Bolzano, Italy (5) Dept of Mental Health, Azienda ULSS, Florence, Italy (6) Agenzia Sanitaria e Sociale Regionale, Regione Emilia Romagna, Modena (Italy) (7) Dept of Mental Health, Azienda ULSS, Bologna, Italy (8) Azienda Ospedaliera Ospedale Niguarda Ca' Grande, Milan Programma 2000, Italy (9) DISM, Inter-Univ Center for Behavioural Neurosciences, Univ of Udine, Udine, Italy

Background: Abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis activity, such as high cortisol levels during the day and a blunted cortisol awakening response, have been previously reported in subjects at their first episode of psychosis (FEP) (Mondelli et al., 2010, Schizophr. Res., 116: 234–242). Childhood traumatic experiences have also been associated with the development of abnormal HPA axis activity (Fisher et al., 2009, Br. J. Psychiatry, 194:319 – 325). Interestingly, previous reports have shown an increased rate of childhood traumatic experience in patients with psychosis (Read et al., 2005, Acta Psychiatr Scand;112:330-50). The aim of our study was to test the association between childhood traumatic experiences, in particular physical abuse, and cortisol levels in a cohort of FEP patients. Methods: We recruited 70 FEP patients (gender: 64% males; age, mean±SEM: 29±1.2 years) as part of the large randomized multi-center controlled study Genetic Endophenotypes and Treatment: Understanding Early Psychosis (GET UP) (Ruggeri et al., 2012 Trials, 13:73). Saliva samples were collected in all subjects to measure salivary cortisol at different time points of the day: at awakening, 15, 30 minutes after awakening, at noon, and at 8pm. We collected information about childhood trauma using the Childhood Experience of Care and Abuse Questionnaire, and divided patients according to presence/absence of severe childhood physical abuse. Differences between abused (n=26) and not abused (n=44) patients were analyzed using repeated measures ANOVA for the cortisol awakening response (0, 15 and 30 minutes post-awakening) and for the diurnal cortisol levels (awakening, noon and 8pm). The results are expressed as mean±SEM. Results: Abused patients showed a trend for higher cortisol levels during the day when compared with non-abused patients (F=3.5, p=0.06). In contrast, abused patients did not appear to show a significant difference in the cortisol awakening response when compared with non-abused patients in the repeated measures analysis (F=0.1, p=0.8). However, when looking directly at the difference in the cortisol rise at 30 minutes after awakening, abused patients appeared to have a blunted cortisol awakening response compared with non-abused patients, although this did not reach statistical significance (delta levels 30-0 minutes: 16.4±11.7 vs 40.2±12.0 pg/ml, p=0.19). Conclusion: Our findings suggest a possible role of childhood physical abuse on the HPA abnormalities, such as the increased cortisol levels during the day and the blunted cortisol awakening response, which have been previously reported in first episode psychosis. None financial sponsorship.

MD06

DIFFERENCES IN HYPOTHALAMIC-PITUITARY-ADRENAL AXIS ACTIVITY AND BRAIN STRUCTURE BETWEEN FIRST EPISODE PSYCHOSIS PATIENTS EXPOSED AND NON-EXPOSED TO CHILDHOOD TRAUMA

Ciufolini S, Dept of Psychosis Studies, Inst of Psychiatry, King’s College London, 16 De Crespigny Park Denmark Hill, SE5 8AF, simone.ciufolini@kcl.ac.uk

Mondelli V(2), Kempton M(1), Reis-Marques T(1), Taylor H(1), Morgan C, Reinders S(1), Murray R(1), David A(1), Pariante C(2), Dazzan P(1) (1) Dept of Psychosis Studies, IoP King’s College London (2) Dept of Psychological Medicine, IoP King’s College London

Introduction: Our body responds to stress activating a system called the Hypothalamic-Pituitary-Adrenal (HPA) axis, which produces the main stress hormone, cortisol. Abnormalities in cortisol levels are found in individuals with psychosis and traumatic experience in childhood. Furthermore, individuals with psychosis and childhood adversity also show brain structure abnormalities. Unfortunately, many due to the use of relatively small samples, whether brain structure and cortisol abnormalities influence each other in the development of psychosis is unclear. Methods: We investigated the effect of childhood trauma on two biological systems: the Hypothalamic-Pituitary-Adrenal (HPA) axis (by measuring the cortisol awakening response) and brain structure using MRI. We evaluated 166 first episode psychosis (FEP) patients (90 trauma-exposed; mean age ± SD 30±9.5 years) and 134 healthy controls (32 trauma-exposed; mean age 32.3±4.5 years). Results: Childhood trauma had an effect on cortisol awakening response in FEP patients as well as in controls (F(3)=4.602 p=0.03 ω2 =0.59), specifically post hoc analysis showed that exposed controls had higher cortisol level at awakening when compared with cases with and without exposure (p = 0.015 and p=0.012 respectively). Trauma-exposure was associated with alterations in gray matter volume in the anterior cingulate gyrus. However, a groupXexposure interaction revealed that the effect of trauma on the right cingulate and right lingual gyrus may differ in individuals who develop and do not develop psychosis (all p<0.001 uncorrected). Conclusions: These preliminary results suggest that exposure to childhood trauma in people with psychosis may reduce their already blunted HPA axis response to a mild stressor, while controls with history of trauma show an increased HPA axis reactivity. Furthermore, the analysis shows differences in brain structure between patients never exposed and patients exposed to trauma, highlighting a potential relationship between childhood trauma and brain volumes. This may suggest that brain structure and cortisol abnormalities may work together in increasing the risk of developing psychosis. This study has been supported by Wellcome Trust and National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King’s College London.
ABSTRACTS

MD07

CORTISOL AND COGNITION IN POSTPARTUM PSYCHOSIS

Hazelgrove K, Psychosis Studies, Inst of Psychiatry, King’s College London, 16 De Crespigny Park London, SE5 8AF, katie.1.hazelgrove@kcl.ac.uk

Hazelgrove K(1), Pawlby S(1), Pauls A(1), Vecchio C(1), Pariante CM(1), Dazzan P(1) (1) Inst of Psychiatry, King’s College London, De Crespigny Park, London SE5 8AF

Background: Psychosis unrelated to gestation is characterised by a dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, in particular a blunted cortisol awakening response and increased cortisol during the day (Mondelli et al., 2010, Schizophrenia Research, 116, 234-242). Furthermore, this blunted cortisol awakening response, found in patients with psychosis unrelated to gestation, has been found to be associated with poorer verbal memory (Aas et al., 2011, Psychological Medicine, 41(3), 463-476). Our research group has also reported increased cortisol awakening response and higher daily cortisol levels in women with and at risk of postpartum psychosis (PP) compared to controls. The aim of this study was to replicate our previous findings and to investigate cortisol awakening response and cortisol levels during the day in relation to verbal memory in a sample of women with and at risk of PP. Methods: 29 women were assessed on average 14 weeks following delivery (range 3 – 43). 7 women had PP, 12 were at risk of PP and 10 were controls. Participants completed assessment of HPA axis (cortisol awakening response and cortisol levels during the day). Verbal memory was assessed using the WMS-III logical memory task (Wechsler, 1997). Results: There was no significant difference between the 3 groups in cortisol awakening response, as indicated by delta cortisol at 15 and 30 minutes. However, there was a significant difference between the 3 groups in daily cortisol levels, as indicated by AUC, with women with PP and at risk of PP having higher daily cortisol levels than healthy controls (M = 52.9, SD = 30.4; M = 76.5, SD = 97.9; M = 32.9, SD = 9.6, respectively; K-W(2) = 8.1, p = 0.017). There was no significant difference between the 3 groups in immediate or delayed logical memory performance. Furthermore, there were no significant correlations between the cortisol awakening response or the daily cortisol levels and immediate or delayed logical memory. Conclusion: Unlike individuals with psychosis unrelated to gestation, we did not find a difference in cortisol awakening response in women with and at risk of PP compared to healthy controls. Furthermore, neither cortisol awakening response nor daily cortisol levels were associated with poorer verbal memory in PP groups. However, in line with previous findings, we did show that women with and at risk of PP had higher daily cortisol levels compared to healthy controls. Funding is provided by the National Alliance for Research on Schizophrenia and Depression (NARSAD) and the MRC/Medical Research Foundation (MRF).

IMMUNE RESPONSE TO STRESS IN POSTPARTUM PSYCHOSIS

Marino M, Inst of Psychiatry, King’s College London, Dept of Psychiatry Studies, PO63. De Crespigny Park, London, SE58AF, monica.marino@kcl.ac.uk

Marino M(1,2), Giordano A(1), Hazelgrove K(1), Vecchio C(1), Pauls AM(1), Mondelli V(1), Mehta MA(1), Aguglia E(2), Pariante CM(1), Pawlby S(1), Dazzan P(1). (1) Inst of Psychiatry, King’s College London, De Crespigny Park, SE5 8AF. London, UK (2) UOPI of Psychiatry, AOU Policlinico “G. Rodolico”, Via Santa Sofia 78, 93100. Catania, Italy

Background: Postpartum Psychosis (PP) is a severe psychiatric disorder associated with childbirth (Munk-Olsen T et al. 2006, JAMA 2006; 296:2582-2589). PP is considered predictable: up to 50% of women with a history of bipolar or schizoaffective disorder or up to 70% of women with a previous history of PP will suffer PP after giving birth (Jones I et al. 2001, Am J psychiatry 2001; 58:913-917). Although PP occurs in conjunction with the biological changes of childbirth, its neurobiological basis is still poorly understood. Stress and inflammation may play a role in the development of Postpartum Psychosis, but little research has been done in both areas. The aim of this study was to investigate the role of stress and inflammation, examining the women’s personal perception of stress and biological markers. Methods: Twenty-one healthy women, 16 women at risk of PP and 14 women with PP were included in the study. All of them completed the Perceived Stress Scale, a self-report questionnaire measuring the perception of stress. Samples of blood were collected to measure the high sensitivity-C Reactive Protein (hs-CRP), a marker of inflammation. Results: Women with PP and at risk of PP had higher scores on the Perceived Stress Scale compared to controls (N = 13, M = 19.00, SD = 6.22; N = 16, M = 16.00, SD = 7.75; N = 21, M = 8.48, SD = 7.32, for PP, at risk of PP and controls, respectively; F(2) = 9.87, p < 0.001). Employing the LSD post-hoc test, women with PP showed a hyperactivation of the immune response, with significantly higher hs-CRP level compared with healthy controls (p = 0.039). There was no significant difference in hs-CRP level between women at risk of PP and controls and between women at risk of PP and women with PP. The scores of the Perceived Stress Scale were positively correlated with hs-CRP level (r = 0.297, N = 47, p = 0.042). Discussion: We found higher levels of perceived stress in women with PP and those at risk of PP compared to healthy women. Moreover, biological abnormalities were observed, especially a hyperactivation of the inflammatory system in women with PP but not in women at risk of PP. These results suggest that inflammation may play a role in the onset of PP. Financial Support: The National Alliance for Research on Schizophrenia and Depression (NARSAD) The MRC/Medical Research Foundation (MRF)
MD09

STRESS BIOMARKERS PREDICT POOR TREATMENT RESPONSE IN FIRST EPISODE PSYCHOSIS: A LONGITUDINAL STUDY OF CORTISOL, CYTOKINES AND BDNF LEVELS

**Mondelli V.** Psychological Medicine, Inst of Psychiatry, King’s College London, 125 Coldharbour Lane London, SE5 9NU, valeria.mondelli@kcl.ac.uk


Background: Biomarkers of stress hold great potential as clinical predictors of treatment response in psychosis. This is suggested by the recognized role of stress in precipitating onset and relapse of psychosis, and by the abnormal biological stress response observed at psychosis onset (Mondelli et al., 2010, Schizophr. Res., 116: 234–242). The main aim of our study was to investigate the role of stress biomarkers (i.e. cortisol, inflammatory markers, brain-derived neurotrophic factor (BDNF)) in predicting treatment response at three months follow-up in first episode psychosis patients. Methods: We collected saliva and blood samples in 68 first episode psychosis patients at baseline and after 3 months from first assessment. Saliva samples were collected at multiple time points during the day to measure diurnal cortisol levels and cortisol awakening response. Cytokines and BDNF levels were analysed from serum samples. Patients were divided into Non-Responders (n=38; mean±SEM age: 29.1±1.3 years, 28 males) and Responders (n=30; age: 29.4±1.4 years, 18 males) according to the Remission criteria of the Schizophrenia Working Group Consensus. Independent T-test was applied to test differences in stress biomarkers between responders and non-responders. Results are presented as mean±SEM. Results: At baseline Non-Responders had significantly lower Cortisol Awakening Response (512.2±61.0 vs 705.7±72.7 nmol min/L, p=0.02) and higher interleukin (IL)6 and interferon (IFN)γ levels (respectively, 15.7±4.0 vs 2.9±0.9 pg/ml, p=0.02 and 20.9±6.0 vs 4.2±2.1 pg/ml, p=0.01) when compared with Responders. At 3-month follow-up, Non-Responders still showed significantly lower cortisol awakening response (336.9±72.8 vs 627.5±129.3 nmol min/L, p=0.05) and higher IL6 levels (34.5±12.6 vs 3.1±1.2 pg/ml, p=0.03). Serum BDNF levels did not differ between Responders and Non-Responders at baseline, but they were significantly lower at 3 months follow-up in Non-Responders when compared with Responders (22.2±1.6 vs 26.8±1.3 ng/ml, p=0.03). Conclusions: Stress biomarkers should be considered as possible predictors for treatment response at the onset of psychosis as well as future targets for the development of novel therapeutic agents. Acknowledgments: This research has been supported by the NIHR BRC for Mental Health at the SLaM NHS Foundation Trust and Institute of Psychiatry, KCL.

MD10

HIPPOCAMPAL ABNORMALITIES AND AGE IN CHRONIC SCHIZOPHRENIA: A MORPHOMETRIC STUDY ACROSS THE ADULT LIFESPAN

**Costafreda SG.** Old Age Psychiatry, King’s College London, Inst of Psychiatry, PO 70. De Crespigny Park, London, SE5 8AF, s.costafreda@gmail.com

Pujol N(1-3), Penades R (1-4), Junque C(1-2), Dinov I(7), Fu CHY(6), Catalan R(1-4), Ibarretxe-Bilbao N(8), Bargallo N(2-4), Toga A(7), Howard RJ(5), Costafreda SG(5). 1 Dept of Psychiatry and Clinical Psychobiology, Univ of Barcelona,Spain 2 Inst d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), C/ Villarroel 170. 08036 Barcelona, Spain 3 Clinical Inst of Neurosciences (ICN), Hospital Clinic, C/ Villarroel 170, 08036 Barcelona, Spain 4 Centre for Biomedical Research on Mental Health (CIBERSAM), Instituto de Salud Carlos III, Barcelona, Spain 5 Dept of Old Age Psychiatry, Inst of Psychiatry, King’s College London,London UK 6 School of Psychology, Univ of East London, Stratford Campus, London E15 4LZ 7 Lab of NeuroImaging, Univ of California, Los Angeles, CA, 90095, USA 8 Dept of Methods and Experimental Psychology, Faculty of Psychology and Education, Univ of Deusto, Bilbao, Spain.

Introduction: Hippocampal abnormalities have been demonstrated in schizophrenia (Tamminga CA et al, 2010, Am J Psychiatry;167:1178-93; Small Psychology, Faculty of Psychology and Education, Univ of Deusto, Bilbao, Spain. 5 Dept of Old Age Psychiatry, Inst of Psychiatry, King’s College London,London UK 6 School of Psychology, Univ of East London, Stratford Campus, London E15 4LZ 7 Lab of NeuroImaging, Univ of California, Los Angeles, CA, 90095, USA 8 Dept of Methods and Experimental Psychology, Faculty of Psychology and Education, Univ of Deusto, Bilbao, Spain.

Background: Cognitive and functional deficits, suggesting that hippocampal morphometry may be a biomarker for cognitive decline in older schizophrenia patients. Funding This study was supported by the Emili Letang Award from Hospital Clinic de Barcelona to NP and grants from the Instituto de Salud Carlos III (FIS nº PI 07/0258) and Rio Hortega grant to NP. The Pere Pons Foundation and the Spain Ministry of Education supplied Individual Mobility Grants to NP. SGC is supported by a National Institute of Health Research (NIHR) Academic Clinical Lecturership.
MD11

ANTERIOR CINGULATE CORTEX ABNORMALITIES IN POSTPARTUM PSYCHOSIS: A STRUCTURAL MRI STUDY

Fuste M, Psychosis Studies, Inst of Psychiatry, King’s College London, 16 De Crespigny Park, SE5 8AF, montserrat.fuste@kcl.ac.uk
Lally J(1), Shergill S(1), Bloomfield MAP(1), MacCabe JH(1), Gaughran F(1), Howes O(1) (1) Inst of Psychiatry, Camberwell, London, SE5 8AF, UK

Introduction: Postpartum Psychosis (PP) is the most severe psychiatric disorder associated with childbirth with an incidence of about one per 1000 deliveries (Munk-Olsen JAMA 2006). 30 to 50% of women with a history of bipolar affective disorder, or of schizoaffective disorder, will suffer PP after giving birth; and up to 50-70% of women with a previous history of PP (Jones and Craddock 2001). Although PP occurs in comitance with the biological changes of childbirth its neuroimological basis remains poorly understood. There is no previous study that has evaluated brain structure in women at risk of, or with, PP. The aims of our study were: 1) Examine brain structural differences in women that develop PP episode compared to the ones that don’t develop PP episode and healthy controls. 2) Study possible differences in the amygdala and the anterior cingulate cortex volumes, areas known to be involved in the affective psychosis spectrum, (Morgan et al., 2007). Methods: This is a Cross-sectional study of 21 healthy postpartum women and 24 women at risk of postpartum psychosis. Within this group, 12 developed postpartum psychosis (PP n=8, Bipolar Disorder n=4) and 12 did not develop postpartum psychosis (Bipolar Disorder n=10, Schizoaffactive Disorder n=1, First-degree family history of PP n=1). We applied a Voxel Based Morphometry (VBM) first in a whole brain analysis as an exploratory approach and then a Region of interest analysis of Anterior cingulate Cortex (ACC) and Amygdala to evaluate the differences in brain structure among the 3 groups. Results: The subgroup that developed PP showed a reduction in the Anterior Cingulate Cortex (ACC) volume compared to those who did not develop PP, the results were statistically significant at cluster level, peak value in coordinates (x, y, z) (4,9,29) t=3.36, pFWE -SVC= 0.002 and k= 129, whereas we did not find significant differences in the at risk group (n=24) when comparing with postpartum control group (n=21). Conclusions: These preliminary findings suggest that women with postpartum psychosis show specific volumetric abnormalities in areas relevant to the pathophysiology of affective psychosis. Particularly, we showed for the first time reductions in ACC in the PP episode group compared to the ones that do not develop PP episode but not in the amygdala as we hypothesized previously. This project has been supported by a NARSAD Independent Investigator Award to P. Dazzan. The study has also received funding by the Psychiatry Research Trust and the MRC Medical Research Foundation. M. Fusté has been supported by the Spanish Rio Hortega Fellowship program (2011-2014).

MD12

INVESTIGATING THE PREVALENCE OF NMDA RECEPTOR AUTOANTIBODIES IN TREATMENT REFRACTORY PSYCHOSIS

Beck KE, Dept of Psychosis, Inst of Psychiatry, Camberwell, London, SE5 8AF, UK, SE5 8AF, katherine.beck@kcl.ac.uk
Pauls A(1,2), Reinders S(1), Mehta M(2), Simmons A(2), Williams SCR(2), Pariante C(3), Dazzan P(1) (1) Dept of Psychosis Studies. Inst of Psychiatry, King’s College of London. (2) Centre for Neuroimaging Sciences, Inst of Psychiatry, King’s College of London, (3)Section of Stress, Psychiatry and Immunology and Perinatal Psychiatry, Inst of Psychiatry, King’s College London, UK

INTRODUCTION: N-Methyl-D-Aspartate receptor (NMDA-R) autoantibodies have been described in patients with acute psychosis. We hypothesised that NMDA-R autoantibodies are implicated in the aetiology of treatment refractory psychosis. The aim of this study is to determine the point prevalence of NMDA-R autoantibody seropositivity in patients referred to services for treatment refractory psychosis. METHOD: The primary outcome measure was seropositivity for NMDA-R autoantibodies. A standardised cell based assay was used to detect serum IgG antibodies directed against the NR1 and NR2b subunits of the NMDA-R. This was performed by the Department of Clinical Neurology, John Radcliffe Hospital, Oxford University. Approval for this study came from the Psychiatry Clinical Academic Group Audit committee at South London and Maudsley NHS Foundation Trust, London UK. RESULTS: The sample consisted of forty-three treatment refractory patients (32 males, 11 females; mean age 43.6 years (SD=11.1, range 20-69); schizophrenia, n=36; schizoaffective disorder, n=7). The mean duration of illness was 15.7 years (SD=9.4, range 2-37 years), and all met criteria for refractory illness. 3 individuals were seropositive for IgG antibodies against NMDA-R, giving a point prevalence of 7.0%. All had low serum antibody titres (1:50, 1:50, 1:100) and none displayed the typical clinical course described in anti-NMDA-R encephalitis. CONCLUSION: 3 of 43 (7.0%) patients with treatment refractory psychosis were positive for NMDA-R autoantibodies. This prevalence is similar to that seen in first episode psychosis (4.3%) and in patients experiencing acute relapses of schizophrenia (9.9%). This does not support the hypothesis that NMDA-R autoantibodies specifically underlie treatment refractory psychosis. Some of the seronegative patients with treatment refractory psychosis may have been seropositive for NMDA-R autoantibodies earlier in their illness, and antipsychotic treatment may have decreased antibody titres. Thus we cannot exclude the possibility that these patients may have had NMDA-R autoantibodies earlier in their illness, with effects persisting after NMDA-R antibody production had ceased. All three seropositive patients had low antibody titres, the clinical significance of which remains to be determined. These findings do not support the hypothesis that NMDA-R autoantibodies are a common aetiology in treatment refractory psychosis. Nevertheless, we cannot exclude a role for these autoantibodies in the pathoaoetiology of a subgroup of these patients. The routine testing of antibodies cannot at present be supported, but further investigation may be warranted, given that there is evidence that some patients with psychosis respond to immunomodulatory therapy. Sources of financial sponsorship: This study was funded by a Medical Research Council (UK) grant to Dr. Howes (grant number:MC-A656-5QD30) and the National Institute of Health Research Biomedical Research Council grant to King’s College London.
MD13

KYNURENINE PATHWAY IN PATIENTS WITH PSYCHOSIS – A META-ANALYSIS OF IN-VIVO STUDIES

Napoletano F, Dept of Psychosis Studies, Inst of Psychiatry, 16 De Crespigny Park, London, SE5 8AF, flavia.napoletano@kcl.ac.uk

Ciufolini S (1), Pariante C (2), Mondelli V (2), Dazzan P (1) (1) Inst of Psychiatry, King’s College London, 16 De Crespigny Park, SE5 8AF (2) Inst of Psychiatry, King’s College London, Dept of Psychological Medicine, 125 Coldharbour Lane, London SE5 9NU

Introduction: In line with the hypothesis of glutamatergic hypofunction in psychosis, post-mortem studies show an increased concentration of kynurenic acid (KYNA), an endogenous antagonist of N-methyl-D-aspartate receptor (NMDAR) and of its direct precursor, kynurenine (KYN), in brain tissues of patients with schizophrenia. However, in vivo studies yield conflicting results; furthermore, it remains unclear if antipsychotic treatment affects the levels of these molecules. In order to understand whether KYN and KYNA concentrations are altered in patients with psychosis, we completed a meta-analysis of existing studies; moreover, we investigated the potential effect of antipsychotic (AP) treatment on KYNA levels in a subsample of studies. Methods: A literature search in PubMed using key words and MeSh terms such as kynurenine pathway, kynuramine, kynurenine, kynurenic acid, quinolinic acid, 5-hydroxytryptamine, schizophrenia, psychosis, delusion, hallucination was performed. Out of 190 studies identified, 48 involved human subjects and 9 provided sufficient information for the meta-analysis. Three measured KYNA concentration in Cerebrospinal Fluid (CSF) in patients with schizophrenia and healthy controls (age: 31.4 (range 18-55); 100% males), 3 evaluated CSF KYNA level in drug-naïve patients and individuals treated with APs (age: 27.5 (range: 18-55); 100% males) and finally 3 studies quantified plasmatic KYN concentration in patients with psychosis and healthy controls (age: 31.3 (range: 14-74); 45.1% males). Methodological quality of all studies was assessed according to specific quality criteria. Pooled effect size (Hedges’s g) was obtained. Results: Individuals with schizophrenia showed a higher level of KYNA in CSF compared with controls (g=0.61 95% CI: 0.32, 0.89; p=<0.001 heterogeneity chi2=2.05 p=0.36), while there was no difference in plasmatic KYN concentration between individuals with and without psychosis (g=-0.98 95% CI: -2.73, 0.77; p=0.27; heterogeneity chi2=90.82 p=0.00). No significant difference in CSF KYNA levels was found in drug-naïve patients when compared with individuals treated with AP medications (g=-1.23 95% CI: -3.22, 0.75; p=0.22; heterogeneity chi2=23.62 p=0.00). Conclusions: The few in vivo studies on the kynurenine pathway in psychosis suggest that CSF level of KYNA, but not plasmatic level of KYN, is increased in patients with psychosis. AP treatment does not seem to affect the CSF level of KYNA. Notwithstanding the small number of studies, these findings point to an alteration of the kynurenine pathway in psychosis, in line with the hypothesis that an excess of KYNA, by reducing the activity of the NMDAR, may play a role in the pathogenesis of schizophrenia.

MD14

ELEVATED ANTERIOR CINGULATE CORTEX GLUTAMATE LEVELS ARE ASSOCIATED WITH ANTIPSYCHOTIC TREATMENT RESISTANCE

Mouchlianitis E, Psychiatric Imaging, MRC Clinical Sciences Centre, Imperial College London, Hammersmith Hospital, Du Cane Rd, W12 0NN, elias.mouchlianitis@csc.mrc.ac.uk

Bloomfield MPA(1), Law V(1), Beck K(2), Selvaraj S(3), Demjaha A (2), Stone JM(2), Howes OD(1) (1)MRC Clinical Sciences Centre, Imperial College, London, UK (2)Inst of Psychiatry, King’s College, London, UK (3)Dept of Psychiatry and Behavioral Sciences, Univ of Texas, Houston, USA

Introduction: Approximately one third of schizophrenia patients are treatment resistant, that is they show limited or no response to repeated treatments with antipsychotic medication. The neurobiological basis for treatment resistance is unknown but recent evidence implicates glutamategic function. We therefore aimed to systematically test this, also in relation to grey matter volume and clinical symptoms Methods: We acquired 1H-MRS spectra at 3 Tesla in the anterior cingulate cortex from 21 treatment-resistant and 20 responsive schizophrenia patients. All participants had a DSM-IV diagnosis of schizophrenia. Treatment resistant patients were classified using the modified Kane criteria. The groups were matched for age, sex, smoking status and illness duration. Results: Glu/Cr levels were increased in resistant patients (Mean (sd)=1.57 (0.24)) compared to responsive patients (Mean(sd)=1.38 (0.23)), with an effect size of d=0.76, (T(35)=2.34, P=0.025). No differences were found in grey matter volume and not correlation with clinical symptoms (P>0.1). Conclusions and relevance: Increased anterior cingulate glutamate levels in treatment-resistant patients may underlie treatment-resistant schizophrenia. This potentially explains the failure of these patients to respond to antipsychotic treatments, which are all dopamine D2 blockers, and suggests glutamategic treatments may be effective in this group of patients. Supported by grant U.1200.04.007.00001.01 from the Medical Research Council, UK.
**MD15**

**EFFECT OF PSYCHOTROPIC DRUGS ON HEART RATE CORRECTED QT INTERVAL (QTc): A NATURALISTIC RETROSPECTIVE STUDY ON A COHORT OF ACUTE PSYCHIATRIC INPATIENTS**

**Romano GF**, Dept of Psychol Medicine, Inst of Psychiatry, King’s College London, Stress, Psychiatry and Immunology Lab, Room 2-055, The James Black Centre 125 Coldharbour Lane London, SE5 9NU, graziella.romano@kcl.ac.uk

**Salviati M(I), Panico R(1), Mondelli V(2), Pariante CM(2), Biondi M(1) (1) Dept of Neurol. and Psychiatry, Sapienza Univ of Rome, Viale dell’Università 30, 00185 Rome, Italy. (2) Inst of Psychiatry, Dept. of Psychol Med, King’s College London, SE5 9NU London, UK

Introduction: Over the past few years, the increasing evidence of the arrhythmogenic action of psychotropic drugs has led to a change in prescribing guidelines for patients with psychosis. In particular, the new guidelines advice to avoid the administration of i.v. antipsychotic treatment, to perform an assessment of the heart rate corrected QT interval (QTc) before and after starting antipsychotic treatment (Wenzel-Seifert K. et al. Dtsch Arztleh Int. 2011 Oct;108(41):687-93.). In this study we investigated the effect of oral antipsychotic treatment on corrected QT interval (QTc) in psychiatric inpatients before and after hospitalization in Acute Psychiatric Ward. Methods: This retrospective naturalistic study was conducted by using data from cases admitted to the Unit of Psychiatry and Clinic Psychopharmacology, Acute Psychiatric Ward (SPDC) of Policlinico Umberto I University Hospital in Sapienza University of Rome. Of more than 900 cases, only 98 fulfilled the following inclusion criteria: 1) minimum of five days of hospitalization, 2) administration of oral antipsychotic treatment, 3) ECG and calculation of heart rate corrected QT interval (QTc) at time of both admission and discharge from the ward, 4) evaluation of electrolytes blood levels, 6) aged over 18 years, 7) signed informed consent to the use of personal data. Statistical analysis was conducted by using the software Statistical Package for Social Sciences version 19.0 (SPSS19). Statistical significance was defined as P<0.05. Results: We observed an overall significant QTc reduction after hospitalization (Δ QTc mean ± SD: -17.6 ± 36.5; P<0.001). We found a significant QTc reduction with Olanzapine (Δ QTc mean ± SD: -28.6 ± 39.3; P<0.001), Aripiprazole (Δ QTc mean ± SD: -18.2 ± 36.5; P<0.05), Risperidone (Δ QTc mean ± SD: -23.3 ± 44.02; P<0.05) and Haloperidol (Δ QTc mean ± SD: -24.9 ± 34.8; P<0.05). We found QTc prolongation during hospitalization in less than 1/3 of the total sample, 8 of the 9 patients who showed a clinically relevant prolonged QTc were receiving Clozapine. Haloperidol was found to be the only antipsychotic showing a dose dependent correlation with QTc prolongation. Conclusions: Antipsychotic treatment alone is not enough to induce a severe QTc prolongation (Chugh SS et al. 2009, Circulation, 119(5):663-70.; Nelson S, Leung J 2011 Oct-Dec, AACN Adv Crit Care, 22(4):289-95.). The overall care of patient, from a clinical and psychiatric point of view, seems to lead to a reduction of arrhythmic risk. The authors declare no financial sponsorship.

**MD16**

**EFFICACY OF LURASIDONE IN THE TREATMENT OF SCHIZOPHRENIA WITH PROMINENT NEGATIVE SYMPTOMS: A POST-HOC ANALYSIS OF SHORT-TERM TRIALS**

**Pikalov A**, Clinical Development, Sunovion Pharmaceuticals Inc., 1 Bridge Plaza North Suite 510, Fort Lee, NJ, USA, 07024, Andrei.Pikalov@sunovion.com

**Schooler NR(1), Hsu J(2), Cucchiario J(2), Goldman(2), Loebel A(2) (1) Dept of Psychiatry and Behavioral Sciences, SUNY Downstate Medical Center, Brooklyn, NY, USA (2) Sunovion Pharmaceuticals Inc., Fort Lee, NJ, and Marlborough, MA, USA

Introduction: Negative symptoms in schizophrenia are associated with poor functional outcome and reduced quality of life. The aim of this post-hoc analysis was to evaluate the efficacy of lurasidone in patients with prominent negative symptoms hospitalized for an acute exacerbation of schizophrenia. Methods: This post-hoc analysis utilized pooled data from five 6-week, double-blind, placebo-controlled trials of patients (N=1532) with an acute exacerbation of schizophrenia who were randomized to fixed, once-daily oral doses of lurasidone in the range of 40-160 mg. Patients with prominent negative symptoms at baseline were identified based on the following criteria: a PANSS negative subscale score ≥25 (median score); and a PANSS positive score <25 (median score). MMRM analyses were performed for change in PANSS total, negative subscale and CGI-S scores; and Cohen’s d effect sizes were calculated. Responder status was evaluated for the PANSS total, defined as reduction from baseline of ≥20%, ≥30%, or ≥40% (LOCF-endpoint); and number needed to treat (NNT) was calculated. Results: 16.7% of patients met criteria for prominent negative symptoms. Treatment of the prominent negative symptom group with lurasidone (vs placebo) was associated with significantly greater week 6 improvement in the PANSS total score (-23.2 vs -13.5; p<0.001), PANSS-negative subscale score (-6.3 vs -4.5; p<0.01), and CGI-S (-1.3 vs -0.8; p<0.001). Week 6 effect sizes (lurasidone vs placebo), were similar for the groups with vs without prominent negative symptoms on the PANSS total score (d=0.46 vs 0.52), PANSS-negative subscale score (d=0.48 vs 0.46), and on the CGI-S (d=0.48 vs 0.46). Week 6 PANSS total score responder rates yielded similar NNT values for the groups with vs without prominent negative symptoms using the PANSS 20% criterion (NNT=6 vs 6), 30% criterion (NNT=5 vs 6), and 40% criterion (NNT=7 vs 8). Discontinuation due to adverse events, for lurasidone vs placebo, respectively, in the prominent negative symptom group was 6.3% vs 2.1%. In the prominent negative symptom group, the most common adverse events reported in at least 15% of lurasidone patients and greater than placebo were headache (22.0% vs 14.4%), somnolence (22.0% vs 4.1%), insomnia (18.2% vs 16.5%) and akathisia (15.1% vs 3.1%). Conclusions: Patients with prominent negative symptoms at baseline responded to lurasidone with significantly improved PANSS total and negative subscale scores, and responder rates that were significantly higher (vs placebo) and comparable to the group without prominent negative symptoms. Lurasidone was well-tolerated in the prominent negative symptom group. Sponsored by Sunovion Pharmaceuticals, Inc.
MD17
TREATMENT WITH LURASIDONE OR RISPERIDONE AND METABOLIC SYNDROME STATUS IN PATIENTS WITH SCHIZOPHRENIA: LONG-TERM EXPOSURE AND SWITCHING EFFECT
Newcomer JW (1), Pikalov A(2), Watabe K(2), Cucchiaro J(2), Rajagopalan K(2), Loebel A(2)
(1) Florida Atlantic Univ, Boca Raton, FL, USA (2) Clinical Development and Medical Affairs, Sunovion Pharmaceuticals Inc., One Bridge Plaza North, Suite 510 Fort Lee, NJ, 07024, Andrei.Pikalov@sunovion.com

Introduction: Patients with schizophrenia are at increased risk for developing metabolic syndrome due, in part, to antipsychotic medications that vary in their tendency to contribute to metabolic dysregulation. This post hoc analysis evaluated the effect of long-term treatment with lurasidone or risperidone on metabolic syndrome prevalence. Methods: In a 12-month, double-blind study, outpatients with clinically stable schizophrenia were randomized 2:1 to flexibly dosed, once-daily lurasidone (40-120 mg/d) or risperidone (2-6 mg/d). In the subsequent 6-month, open-label extension, all patients received flexibly dosed lurasidone (40-120 mg/d). Metabolic syndrome was defined using International Diabetes Federation criteria: elevated waist circumference (based on ethnic group-specific norms) or BMI ≥30 kg/m2 plus ≥2 of triglycerides ≥150 mg/dL (1.7 mmol/L), HDL cholesterol <40 mg/dL (1.03 mmol/L) in men or <50 mg/dL (1.29 mmol/L) in women, blood pressure ≥130/85 mmHg, or blood glucose ≥100 mg/dL (5.6 mmol/L). Logistic regression was used to calculate odds ratios; associated p values were based on chi-square tests. Results: At double-blind baseline, metabolic syndrome prevalence was 32.5% (134/412) in the lurasidone group and 32.7% (65/199) in the risperidone group. Metabolic syndrome prevalence (observed cases [OC]) after 12 months of treatment was 31.5% (47/149) with lurasidone and 44.1% (41/93) with risperidone (p<0.05). Among patients without metabolic syndrome at baseline, 16.3% (16/98) of lurasidone-treated patients and 27.1% (16/59) of risperidone-treated patients had metabolic syndrome after 12 months (OC); risk for developing metabolic syndrome was 48% lower for lurasidone-treated versus risperidone-treated patients (odds ratio=0.52; 95% CI, 0.24-1.15). Among patients with metabolic syndrome at baseline, 36.7% (18/49) receiving lurasidone and 28.1% (9/32) receiving risperidone no longer met criteria for metabolic syndrome after 12 months. For patients who took lurasidone in both the double-blind and open-label phases (n=109), metabolic syndrome prevalence was 33.3% at baseline and 26.6% after 18 months of treatment (OC). In patients switched to open-label lurasidone after 12 months of double-blind risperidone treatment (n=65), metabolic syndrome prevalence was 42.9% at baseline, 48.4% after 12 months on risperidone, and 38.5% after switching to lurasidone for 6 months (OC). Conclusions: Lurasidone treatment was associated with lower risk of metabolic syndrome compared with risperidone treatment. The prevalence of metabolic syndrome remained stable during 18 months of continuous treatment with lurasidone, but increased during 12 months of treatment with risperidone. Switching to lurasidone after 12 months of treatment with risperidone was associated with a decrease in metabolic syndrome prevalence. Study sponsor: Sunovion Pharmaceuticals Inc. ClinicalTrials.gov identifier: NCT00641745

MD18
A DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED WITHDRAWAL STUDY TO ASSESS THE EFFICACY AND SAFETY OF LURASIDONE FOR THE LONG-TERM MAINTENANCE TREATMENT OF SCHIZOPHRENIA
Tandon R(1), Loebel A(2), Phillips D(2), Pikalov A(2), Hernandez D(2), Mao Y(2), Cucchiaro J(2) (1) University of Florida College of Medicine, Gainesville, FLA, USA (2) Clinical Development and Medical Affairs Sunovion Pharmaceuticals Inc., One Bridge Plaza North, Suite 510 Fort Lee, NJ, 07024, Andrei.Pikalov@sunovion.com

Introduction: Long-term treatment for schizophrenia is necessary to minimize the occurrence of psychotic relapse. The objective of this study was to evaluate the effectiveness of lurasidone as a long-term maintenance treatment for schizophrenia. Methods: Patients 18 to 75 years of age, diagnosed with schizophrenia and currently experiencing an acute psychotic exacerbation were initially enrolled into a 12- to 24-week, open-label, stabilization phase in which they received flexibly dosed lurasidone (40-80 mg/d). Patients who responded to open-label lurasidone treatment and achieved ≥12 weeks of clinical stability entered the 28-week, double-blind, withdrawal phase and were randomized to either continue receiving lurasidone (initially at the final stabilization dose, then flexibly dosed [40-80 mg/d]) or were switched to placebo. Kaplan-Meier survival curves were generated and the primary endpoint of time to relapse was analyzed using log-rank test and Cox proportional hazards model. The nominal p value for designating statistical significance was adjusted from 0.05 to 0.042 due to prespecified unblinded interim analyses. Secondary outcomes included change from baseline PANSS and CGI-S scores, treatment-emergent adverse events (TEAEs), and change in weight and metabolic parameters. Results: Of the 676 patients enrolled in the open-label stabilization phase, 285 met stabilization criteria and were eligible for randomization to lurasidone (N=144) or placebo (N=141). Among randomized patients, mean PANSS total score decreased from 90.1 at open-label baseline to 54.4 at double-blind baseline, indicating substantial symptomatic improvement during the open-label phase. Time to relapse was significantly delayed (log-rank test, p=0.039) and the risk for relapse was reduced by 33.7% for lurasidone-treated patients versus placebo (Cox model HR [95% CI], 0.663 [0.447-0.983]; p=0.041) during the double-blind phase. Patients receiving placebo experienced significantly greater clinical worsening based on mean change in PANSS and CGI-S scores over the double-blind period compared to lurasidone-treated patients (PANSS, +12.4 vs +8.3 [p=0.029]; CGI-S, +0.7 vs +0.4 [p=0.015]; LOCF). The most common AE reported in patients treated with lurasidone for the entire study (open-label phase through double-blind phase) were akathisia, insomnia, headache, nausea, and anxiety. Discontinuation rates due to TEAEs in the double-blind phase were 13.9% for lurasidone and 15.6% for placebo. Both groups experienced minimal changes in weight and prolactin, lipid, and glucose parameters. Conclusions: This study demonstrated the effectiveness of lurasidone for maintenance treatment of patients with schizophrenia. Long-term lurasidone treatment was generally well tolerated and produced minimal effects on weight and other metabolic parameters. Study sponsor: Sunovion Pharmaceuticals Inc. ClinicalTrials.gov identifier: NCT01435928
MD19

FIVE YEAR PATIENT OUTCOMES WITH RISPERIDONE LONG-ACTING INJECTION OR ARIPIPRAZOLE

Deslandes PN, Pharmacy Dept, Whitchurch Hospital, Park Rd, Cardiff, CF14 7XB paul.deslandes@wales.nhs.uk
Dwivedi M (2), Sewell RDE (2) (2) School of Pharmacy and Pharmaceutical Sciences, Cardiff Univ, Cardiff CF10 3NB

Introduction: The antipsychotics risperidone long acting injection (RLAI) and aripiprazole have been available in the UK since October 2002 and July 2004 respectively. When launched, both represented novel approaches to the treatment of psychosis. This study examined five year outcomes of patients prescribed RLAI or aripiprazole in a clinical setting, using treatment discontinuation as a measure of effectiveness. Method: Patients who received RLAI or aripiprazole in the 18 months following their respective UK launches were included. Two year outcome data has previously been reported for these cohorts (Deslandes et al. 2009 Int J Psychiatry Clin Pract 13:298-302 and Deslandes et al. 2010 J Psychopharmacol 24 (suppl 3): A14). The current study reports an additional three years of follow-up for each group. The number of patients remaining on treatment at two years (and included in this study) was 28/84 and 27/92 for RLAI and aripiprazole respectively. Data were collected from pharmacy records and by retrospective case note review. Patients were classified as continuers or discontinuers at five years, and reasons for treatment discontinuation noted. Six patients treated with RLAI and eight treated with aripiprazole had previously received clozapine. Results: Of the 55 patients included, two treated with RLAI and three treated with aripiprazole were lost to follow-up. Therefore, five year outcome data were available for 50 patients (26 RLAI and 24 aripiprazole). Fifteen patients from each group were continuers at five years. Of the 30 continuers, four patients receiving RLAI and three receiving aripiprazole were co-prescribed other antipsychotics at endpoint. Three of the four prescribed RLAI received oral risperidone as the second antipsychotic. Four patients remaining on RLAI and two remaining on aripiprazole at five years had previously received clozapine. Reasons for discontinuation of RLAI and aripiprazole respectively were lack of effect (n=4; 4), adverse effects (n=3; 1), non-compliance or patient choice (n=2; 4), and patient death (n=2; 0). Conclusions: There was no significant difference between the proportions of patients continuing RLAI or aripiprazole for five years. Continuation rates were relatively low (18% and 16% of the original RLAI and aripiprazole cohorts respectively), whilst co-prescription of other antipsychotics was relatively common (23% of continuers). Reasons for discontinuation were comparable, with lack of effectiveness the most common reason for both compounds. These findings suggested that clinical effectiveness was somewhat disappointing, although the long period of follow-up and large number of previously clozapine treated patients in the original cohorts were confounding factors.

Sources of funding: None

Acknowledgements: The authors thank Mrs W. Davies for the opportunity to conduct this work.

D20

MEDICATION ADHERENCE AIDS IN MENTAL HEALTH AND SCHIZOPHRENIA: A SYSTEMATIC REVIEW

Coates J, Rotherham, Doncaster and South Humber NHS Foundation Trust, Rotherham General Hospital, Moorgate Rd, Rotherham, S60 2UD, mstead@mednet.co.uk
Stead M (1) Bahoochy (1) Dodd (2) (1) 40 Otley Rd, Leeds LS6 2AL (2) Quantum House, Hobson Industrial Estate, Burnopfield, Co. Durham NE16 6EA.

Aims: The Biodose Connect has been created as an innovative, tailored service that combines the latest technology in connected health with the support of care professionals to enhance medicines adherence. The company behind Biodose Connect wishes to develop an evidence base for the service in mental health and in particular schizophrenia. A systematic review was conducted to identify studies of adherence support in this field.

Background: Enhanced adherence to prescribed medication is a key goal leading to enhanced clinical outcomes associated with benefits for both patient, NHS Commissioners and clinical teams alike. Patients spending less time in the healthcare system may lead to reduced costs. Methods: We searched Pubmed for papers published between March 2007 and February 2014. The inclusion criteria consisted of: - studies with humans involved in medication adherence interventions in schizophrenia - or psychiatric patients. Data collection and analysis Two independent review authors screened and extracted information. Results: Four papers were selected, two of these were randomised controlled studies; one investigating the efficacy of a pill dispenser (Randomised controlled trial with a Canadian electronic pill dispenser used to measure and improve medication adherence in patients with schizophrenia. Frontiers in Pharmacology, Vol 4, Article 100), one studying text reminders to enhance adherence (Montes, J., Medina, E., Gomez-Beneyto, M. and Maurino, J. (2012). A short message service (SMS)-based strategy for enhancing adherence to antipsychotic medication in schizophrenia. Psychiatry Research, 200, pp. 89-95). Both protocols had beneficial outcomes for patient adherence. One study investigated the validity and reliability of using an electronic monitoring bottle cap in collecting data of user adherence and found the tool to be effective (p<0.002) (Nakonezny, P., Byerly, M. and Rush, J. (2007). Electronic monitoring of antipsychotic medication adherence in outpatients with schizophrenia or schizoaffective disorder: An empirical evaluation of its reliability and predictive validity. Psychiatry Research, 157, pp. 259-263) and a survey of psychiatric inpatient views on SMS medication reminders (Bogart, K., Wong, C., Akenzua, A., Hayes, D., Prountzos, A., Okocha, C. and Kravariti, E. (2014). Mobile phone text message reminders of antipsychotic medication: is it time and who should receive them? A cross-sectional trust-wide survey of psychiatric inpatients. BMC Psychiatry, 14, 15). Conclusions: Little research has been conducted in the field of schizophrenia and medication adherence. From the available literature, simple tools have shown promise in enhancing adherence and recording compliance. A multi-method adherence aid such as Biodose Connect could therefore increase adherence further and provide accurate data to clinicians. Further research in this field is needed. Quantum Pharmaceutical Group sponsored the development of this abstract.
MD21

NEW MEDICATION IN ADULT ACUTE PSYCHIATRIC WARDS - ARE PATIENTS GIVEN ADEQUATE INFORMATION AND CHOICE?

**Sorensen EH**, Univ of Birmingham, Medical School, Edgbaston, Birmingham, B15 2TT ehs961@bham.ac.uk

McKee EK (1), Brownell L (2) (1) Medical Student, Medical School, Univ of Birmingham, Edgbaston, Birmingham B15 2TT (2) Yewcroft Centre, Court Oak Road, Harborne, Birmingham B17 9AB

Introduction: Patient autonomy is a pillar of modern medicine, and is key to maintaining the relationship of trust between doctor and patient. It is widely recognised that a lack of shared decision making is directly linked to non-adherence to treatment. Non-adherence to psychiatric medications is associated with increased risk of psychotic relapse, hospital admission, danger to the patient and others, and poor long term outcomes. The standards of information sharing and patient decision making, which ought to be observed in all medical settings and in psychiatry, are set out in NICE clinical guidelines CG76 and CG136 respectively. The aims of this audit are to discover if and to what extent inpatients within the Birmingham and Solihull Mental Health NHS Foundation Trust (BSMHFT) are given adequate choice regarding their treatment, and whether they are given adequate information about new medications in order to make an informed choice. Methods: This was a retrospective postal-questionnaire based study, based on standards extracted from NICE CG76 and 136. The questionnaire was sent to all patients discharged from general adult acute psychiatric wards within the BSMHFT in August and September 2013. The responses from returned questionnaires were compiled and analysed. Results: 43 out of 303 questionnaires were returned. 27 out of these 43 (62.8%) reported that they had started a new drug while in hospital. The average satisfaction score was 42%. Patient feedback was well below the target of 100% positive for all questions. Discussion: There are significant deficits in both information sharing and decision making opportunities. This is likely to have significant impacts on the doctor-patient relationship, and will affect compliance and concordance both while in hospital and after discharge. From the results of this audit our recommendations are: - a more structured approach to starting new medications needs to be taken. This could be in the form of a “new medication form” which could include a checklist of tasks. This could allow formal agreement between doctor and patient, and give permanent documentation regarding all discussion. A copy should be given to patients. - On a similar note, compulsory documentation (possibly with a similar form) within online patient records could be used to remind healthcare professionals of the need for these discussions. - The trust could produce simple printable leaflets with the key information for commonly used drugs. This will save time and ensure that standardised information is given to all patients.

MD22

CLOZAPINE AUGMENTATION: AN INVESTIGATION OF CURRENT PRACTICE

**Sheehan R**, Camden and Islington NHS Foundation Trust, Camden Learning Disabilities Service, 3rd Floor Bidborough House, 38-50 Bidborough St, London, WC1H 9BT, rory.sheehan@hotmail.com

**Killaspy H** Div of Psychiatry University College London 1st Floor Charles Bell House 67-73 Riding House St London W1W 7EJ

INTRODUCTION: Even with optimum clozapine treatment, only 30 to 60% people with treatment-resistant schizophrenia will have a satisfactory response. Augmenting clozapine with other drugs is relatively common practice. Despite this, there is limited evidence to suggest which pharmacological augmentation strategies are most effective. Frequent augmentation agents are a second anti-psychotic, an anti-depressant, or a mood stabiliser. We audited current practice in clozapine augmentation within our Trust, investigated factors associated with augmentation, and identified a proportion of patients who may benefit from augmentation. METHODS: A register of all community patients prescribed clozapine in Islington was obtained from the pharmacy at Highgate Mental Health Centre. A list of each patient’s current medication was retrieved from the electronic patient record system (RiO6), or if no complete list was available, GPs were asked to provide details. HoNOS scores are clinician-rated measures of patient problems in several psychosocial domains. Each patient’s most recent HoNOS score of delusions / hallucinations (item 6) and depressed mood (item 7) was recorded as a measure of symptom burden. Descriptive statistics were obtained on the proportion of patients augmented with clozapine and which agents were used. A multivariable logistic regression analysis was performed to investigate the association between HoNOS scores and augmentation agents. RESULTS: 154 patients were registered with the clozapine clinic in Islington. An accurate medication list was obtained for 144 patients (male: 63.2%, mean age: 45 years). 83 patients (57.6%) were augmented with at least one agent. Our results show the breakdown of augmenting agents by drug class and indicate that mood stabilisers are the most frequently used augmentation agent. Patients with high HoNOS depression scores were more likely to be augmented with an anti-depressant while patients with high HoNOS delusions / hallucinations scores were more likely to be augmented with another anti-psychotic. A significant number of patients with HoNOS scores ≥ 2 were not augmented with an anti-psychotic or anti-depressant. CONCLUSIONS: Our results provide a quantitative description of clozapine augmentation practices in an inner London borough. The majority of patients taking clozapine are augmented. We have identified a ‘treatment gap’ of people who may benefit from augmentation. HoNOS depression score was more strongly associated with augmentation than delusions / hallucinations score, suggesting that clinicians may be more likely to respond to features of depression than persistent positive symptoms by adding additional drugs. FUNDING No funding has been received for this study.
MD23

PLASMA CONCENTRATION THERAPEUTIC DRUG MONITORING FOR OLANZAPINE AND RISPERIDONE: A FEASIBILITY STUDY

Patel MX, Dept of Psychiatry Studies, Inst of Psychiatry, KCL, 16 DeCrespigny Park PO68, London, SE5 8AF, maxine.patel@kcl.ac.uk
Law S(1), Gudbrandsen M(1), Magill N(1), Rose D(1), Flanagan RJ(2), David AS(1) (1)Inst of Psychiatry, KCL, 16 DeCrespigny Park, London, SE5 8AF; (2) Toxicology Unit, King’s College Hospital, London, SE5 9RS

Background: Therapeutic drug monitoring (TDM), which examines drug plasma concentrations, is a potentially useful objective tool to aid in the optimisation of antipsychotic prescribing. This study aimed to develop and test a clinically acceptable method for olanzapine and risperidone TDM. Method: A non-randomised feasibility study recruiting inpatients from 5 Mental Health Trusts in South-East England was conducted. The intervention comprised: (i) a blood sample taken 12 hours post dose for TDM analysis, 7-14 days after initial drug initiation; (ii) rapid feedback of TDM results to clinicians accompanied by a newly developed algorithm offering interpretation and advice for individual patient antipsychotic dose management. The algorithm was based on target ranges and the time to steady state (olanzapine 20-40ng/mL, 7 days; risperidone 20-60ng/mL, 5 days). A baseline assessment and 6-week follow-up review of clinical notes was conducted to ascertain change in total daily dose of the target drug and to evaluate the TDM process. Results: Of the 22 consenting participants on olanzapine 19 provided a blood sample, for whom 17 TDM results were made available by the lab, and only 14 remained on olanzapine at study end. Of the 13 consenting participants on risperidone, all provided a blood sample, for whom only 12 TDM results were made available by the lab and only 9 remained on risperidone at the end of the study. There was a mean increase in olanzapine dose of 0.9mg/day (S.D. 2.7, range 0-10) and a mean decrease in risperidone dose of -0.3mg/day (S.D. 2.0, range -4-3). However, only seven (24.1%) participants experienced a dose change, of which only four (13.8%) of the TDM results were confirmed as having been checked by the clinician. Trough level sampling was achieved for all participants for whom data was available, whereas steady state was only achieved for 25/32 (78.1%) participants. Of the 29 TDM results, 16 (55.2%) were reported on within three working days. Conclusions: TDM can be feasibly implemented as part of routine clinical practice for olanzapine and risperidone. However, there appears to be a ‘vicious circle’ of lack of robust evidence of the advantages of antipsychotic TDM utilisation leading to lack of enthusiasm for checking results and therefore adopting TDM even within a clinical trial. Given that clinicians are yet to embrace antipsychotic TDM it is likely that uptake will be gradual. This study was funded by an NIHR Clinician Scientist award for Dr Maxine Patel.

MD24

FEASIBILITY OF A COMBINED COMPUTERISED COGNITIVE REMEDIATION AND SOCIAL COGNITION TRAINING INTERVENTION TO IMPROVE NEUROCOGNITIVE DEFICITS FOLLOWING A FIRST EPISODE OF PSYCHOSIS

Revell ER, Manchester Pharmacy School, Univ of Manchester, Stopford Bldg Oxford Rd, Manchester, M13 9PT, emily.revell@postgrad.manchester.ac.uk
Harte M (1), Drake RJ (1), Brewin A (2), Neill JC (1) (1) Faculty of Medical and Human Sciences, Univ of Manchester, M13 9PT (2) Bradford Early Intervention in Psychiatry Service, Bradford District Care Trust, BD1 2EP

INTRODUCTION: The main predictors of disability following a first episode of psychosis are neurocognitive deficits and negative symptoms, a current unmet clinical need. Cognitive remediation (CR) is a therapy which aims to improve daily functioning and quality of life through improvements in neurocognition. CR produces meaningful, durable improvements in both cognition and functioning (Wykes et al, 2011, Am J Psychiatry, 168, 472–485). However, most CR interventions currently in use do not target social cognition, the most important deficit for social function (Couture et al, 2006, Schizophrenia Bulletin, 32, S44-S63). Moreover, most CR research has been conducted with chronic schizophrenia patients. We intend to examine the benefits of early CR and to compare it to CR plus social cognition training (SCT) in a pilot trial. The first stage of this trial examined the feasibility of conventional CR and CR+SCT following a first episode of psychosis and the results of this are presented here. METHODS: In this stage of the trial, eight participants were randomised to either a ten week CR or CR+SCT group intervention using the computer battery. Functioning and symptoms were measured using the Personal and Social Performance Scale (PSP) and the Positive and Negative Syndrome Scale (PANSS). Participants also provided feedback on the interventions. RESULTS: Those who completed the interventions (n=4) reported high satisfaction with the training. Small improvements were seen in both groups post-intervention, compared to baseline, on Cantab measures of verbal memory (free recall means: T1=6.8, T2=9.5), executive functioning (one touch stockings of Cambridge means: T1=9.8, T2=11.5) and social cognition (emotion recognition means: T1=51.2, T2=57.4). Additionally, symptoms had reduced (PANSS means: T1=59.5, T2=54.2) and functioning improved (PSP means: T1=68.5, T2=79.5). The attrition rate of fifty percent was due to relapse (n=2) and inability to attend the group sessions (n=2). In an attempt to reduce the attrition rate, the interventions will now also be offered as individual sessions. CONCLUSIONS: This stage of the trial has verified that the interventions are feasible and acceptable. Forty further participants will be recruited to explore the effectiveness of the combined intervention compared to CR alone. This research will contribute to the growing field of cognitive remediation literature and will help to determine whether the effects of CR for first episode psychosis patients could be enhanced by adding a social cognition training element. This study is funded by the University of Manchester.
MD25

IMPLICIT VISUAL STATISTICAL LEARNING AND PERCEPTUAL INFERENCE IN CHRONIC SCHIZOPHRENIA

Valton V, Inst of Adaptive and Neural Computation, Univ of Edinburgh, 10 Crichton St, Informatics Forum Edinburgh, Scotland/UK, EH8 9AB, vincent.valton@ed.ac.uk
Lawrie S(1), Seitz A(2), Seriès P(3) (1) Dept of Psychiatry, Royal Edinburgh Hospital, Univ of Edinburgh, UK (2) Dept of Psychology, Univ of California Riverside, CA, USA (3) Inst for Adaptive and Neural Computation, Univ of Edinburgh, UK

Introduction: Recent hypotheses of psychosis suggest that positive-symptoms could stem from learning deficiencies resulting in distorted internal representations of the world (Fletcher & Frith, 2009, Nature Reviews Neuroscience, vol. 10, pp. 48-58). In line with these assumptions, schizophrenic patients have shown to be impaired in statistical learning and probabilistic inference in decision-making tasks (Averbeck et al., 2011, Schizophrenia Research, vol. 127, pp. 115-122). Aim: We here ask whether schizophrenic patients are also impaired in more implicit/perceptual forms of probabilistic inference, such as visual statistical learning. We used a motion task known to induce rapid implicit learning of the statistics of the stimuli (Chalk et al., 2010, Journal of Vision, vol. 10, pp. 2-19). In controls, this learning influences perception in two ways: 1) motion stimuli are perceived as being more similar to the most frequently presented stimuli than they really are (estimation biases); 2) in absence of visual stimuli, participants sometimes report perceiving the most frequently presented stimuli (‘hallucinations’). Such behaviour is consistent with the participants acting as Bayesian observers and combining learned perceptual priors with sensory evidence. We investigated whether schizophrenic patients would differ in their acquisition of the perceptual priors and in how such priors would impact their perception. Method: 11 medicated chronic schizophrenic patients (mean illness duration 14.72 ±2.73 years) and 10 controls were recruited and participated in a single session of the task lasting 40 min.

Results: Although patients were slower than controls, their estimation and detection performances were similar. In particular, patients showed similar acquisition of perceptual priors, approximating the stimulus statistics. Intriguingly, however, patients made on average significantly fewer ‘hallucinations’ of the most frequently presented directions than controls (exact permutation test, p=0.0174). The total amount of ‘hallucinations’ correlated negatively with symptom severity (PANSS Total & Positive scales; p<0.05) and positively with medication dosage (Chlorpromazine equivalent; p<0.05).

Conclusions: This study suggests that chronic (medicated) patients can perform similarly to controls with regards to implicit statistical learning of visual stimuli. Expectations-driven ‘hallucinations’ during the task appear to be linked with symptom severity in patients.

Acknowledgments: This work was funded by the BBSRC, MRC and EPSRC through the Doctoral Training Centre in computational neuroscience of the University of Edinburgh.

MD26

FACIAL AFFECT PROCESSING DEFICITS IN SCHIZOPHRENIA: A META-ANALYSIS OF ANTIPSYCHOTIC TREATMENT EFFECTS

Gabay AS, Dept of Neuroimaging, Inst of Psychiatry, King’s College London, PO 089, De Crespigny Park, London, SE5 8AF, anthony.a.gabay@kcl.ac.uk
Mehta MA(1), Kempton MJ (1), (1) Centre of Neuroimagining, Inst of Psychiatry (PO 089), De Crespigny Park, London, SE5 8AF

Introduction: Social cognition, including emotion processing, is a recognised deficit observed in patients with schizophrenia. It is one domain of cognitive functioning which has been emphasised as requiring further investigation in order to improve functional outcome (Green et al, 2004, Schizophrenia Research, 72(1):41-5). A widely studied aspect of social cognition is emotion processing, which is typically assessed using tasks requiring participants to perceive, identify and discriminate between facial emotion expressions. Methods: Nine studies met our criteria for entry into a meta-analysis of the effects of medication on facial affect processing, including data from 1162 patients and 6 different antipsychotics. Results: Contrary to expectations, we found a small, positive effect, representing an improvement in facial affect processing (Hedge’s g = 0.13, 95% CI 0.02 to 0.21, p =0.002). There was no significant overall between-study heterogeneity (p = 0.85), and no evidence of publication bias (p = 0.49). Hedge’s g was significant for atypical (0.11, 95% CI 0.02 to 0.21, p = 0.01), but not typical antipsychotics (0.17, 95% CI -0.09 to 0.43, p = 0.16). Meta-regression analyses suggested neither age nor gender were moderators (p = 0.13 and p = 0.49, respectively). Meta-regression analyses suggest the same is true for change in positive and negative symptoms (p = 0.83 and p = 0.97, respectively). Conclusions: While both dopaminergic and serotonergic mechanisms have been implicated in emotion processing, the exact mechanism by which these medications effect facial affect processing is uncertain. Although a small, positive effect of antipsychotic medication was found, it is questionable whether this would be clinically significant in terms of treating deficits in emotion identification in schizophrenia, which have been reported to have a Cohen’s d of -0.89, rising to -1.41 when restricted to unmedicated patients (Kohler et al, 2010, Schizophr. Bull., 36(5):1009-19). We show that antipsychotic medications are poor at improving facial affect processing deficits compared to reducing symptoms (Hedge’s g ranging from -0.33 to -0.88; Leucht et al, 2013, Lancet 382(9896):951-62). This highlights the need for further investigation into the neural and neuropharmacological mechanisms associated with accurate emotion processing, to inform further treatment options for these deficits in schizophrenia and other affective disorders.

Acknowledgments: We are very grateful to those authors of included studies who provided additional data. MJK is funded by an MRC Career Development Fellowship (grant number MR/J008915/1). ASG was supported by a joint MRC-IoP studentship.
Introduction: Chronic cannabis use has been implicated in the development of Schizophrenia and this relationship may be mediated by psychosis proneness. Delta-9-tetrahydrocannabinol (THC) produces reliable increases in psychotomimetic symptoms as well as impairments in episodic memory. Cannabidiol (CBD), another major cannabinoid in cannabis, is associated with pro-cognitive effects (Morgan et al., 2012, Psychol Med 42, p.391-400), and can reduce positive and negative symptoms in those with Schizophrenia (Leweke et al., 2012, Transl Psychiatry p. e94). Method: In a randomised, double-blind, placebo-controlled, crossover laboratory study, cannabis users (n=48) selected for high and low frequency of use and schizotypy scores (Schizotypal Personality Questionnaire) were administered a single dose of THC (8mg), CBD (16mg), a combination of THC+CBD (8mg+16mg) or placebo on four separate occasions (1 week wash out). Participants were administered the Psychotomimetic States Inventory (PSI), Brief Psychiatric Rating Scale (BPRS) and immediate and delayed prose recall (episodic memory) on each day. Results: We found interactions between Drug and PSI subscales of Perceptual Distortion (THC: P=0.006; THC+CBD: P=0.005) and Cognitive Disorganisation (THC: P=0.008; THC+CBD: P=0.004). CBD produced no change in comparison to placebo. We found a Drug By Schizotypy interaction suggesting that high Schizotypes scored greater on PSI subscales of Cognitive Disorganisation (P=0.001), Anhedonia (P<0.001), Mania (P=0.004), Paranoia (P=0.007) in comparison to low Schizotypes. We also found a main effect of drug driven by increased scores following THC (P=0.014) and THC+CBD (P=0.022) but not CBD. The BPRS revealed higher scores for Positive relative to Negative items (P=0.02). Both THC and THC+CBD increased scores on Negative items, but not Positive items. We found a main effect of Drug on prose recall reflecting poorer scores after THC (P=0.031) and THC+CBD (P=0.024) relative to placebo, but this was not the case for CBD. We also found a main effect of Delay, reflecting poorer scores in the delay relative to the immediate Prose Recall. Conclusions: Both the PSI and BPRS are sensitive to cannabinoid administration. At a ratio of 2:1, CBD does not attenuate the acute psychotic and memory impairing effects of vaporized THC alone or when combined. Antipsychotic effects of CBD may be lacking in frequent cannabis users, which is of concern due to the high rates of cannabis use in patients with schizophrenia. This research was funding by the Medical Research Council.
ME02

DISRUPTION OF LEARNED ATTENTION IN HIGH-ANXIETY INDIVIDUALS

Granger KG, School of Psychology, Univ of Nottingham, Univ Park Nottingham, NG7 2RD, lpkktgra@nottingham.ac.uk
Haselgrove M(1), Moran P(1) (1) School of Psychology, Univ of Nottingham, University Park, Nottingham NG7 2RD

Introduction: Converging lines of evidence suggest a role for situational, or state, anxiety in the modulation of attention. It has been suggested that increased levels of anxiety result in decreased attentional control, characterised by an increase in distractibility by irrelevant information (e.g., Braunstein-Bercovitz, 2001, Emotion, 1, 182-192; Eysenck et al, 2007, Emotion, 7, 336-353). Based on associative theories of learning, the prior predictive history of a stimulus will affect how well that stimulus is attended to, and thus learnt about in the future (e.g., Mackintosh, 1975, Psychological Review, 82, 276-298; Pearce & Hall, 1980, Psychological Review, 87, 532-552). At this juncture it is unclear what the relationship is between anxiety, and learning about stimuli that have a history of learned predictiveness and irrelevance. Here we report two experiments that investigated the relationship between learned variations in stimulus attention and state-anxiety. Method: For experiment 1 (N=64; 50 females and 14 males, age-range 18-36) we employed a serial visual-processing task and for Experiment 2 (N=88; 68 females and 20 males, age-range 18-54) a contingency-learning task described by Le Pelley, et al. (2010, Learning & Behavior, 38, 120-144). In both experiments participants were first given trials in stage 1 in which different cues signalled one of two outcomes with either 100% accuracy (i.e. predictive) or 50% accuracy (i.e. irrelevant). To assess attention to these cues, in stage 2, both were paired with two novel outcomes under identical conditions (100% accuracy). Participants in each experiment then completed the state-trait inventory for cognitive and somatic-anxiety (Ree et al., 2008, Behavioural and Cognitive Psychotherapy, 36, 313-332). Results: In both experiments we conducted a 2 (state-anxiety: high, low) x 2 (cue: irrelevant, predictive) mixed ANOVA of stage 2 data and observed that learning about the cue that was previously predictive (100%) was higher than the cue that was previously irrelevant (50%), but only in low-anxious participants (p <.05). High-anxious participants showed no difference in learning about these cues (p >.05). Conclusions: High-anxious individuals show an insensitivity to the difference between relevant and irrelevant information; unequal distribution of attention to these cues (based on their prior predictive history), affects how well these cues are learnt about in future learning. These results contribute to existing knowledge regarding an attention deficit in individuals in a transient state of anxiety. Such findings have implications for the continuing progress of treatment for anxiety-disorders, particularly for the development of specific cognitive-training programmes. Financial sponsorship: The Economic and Social Research Council

ME03

ANXIOUS INDIVIDUALS HAVE DIFFICULTY LEARNING THE CAUSAL STATISTICS OF AVERSIVE ENVIRONMENTS

Browning M, Psychiatry, Univ of Oxford, Neuroscience Bldg, Warneford Hospital, Oxford, OX3 7JX, michael.browning@psych.ox.ac.uk
Behrens TE(1) Jocham G (2) O'Reilly JX (1) Bishop SJ (1) (1) FMRIB Centre Oxford (2) Univ of Magdeburg, Germany

Introduction: Statistical regularities in the causal structure of the environment enable us to predict the probable outcomes of our actions. Environments differ in the extent to which action-outcome contingencies are stable or volatile [1]. It is thought that adaptation of learning in stable vs. volatile environments is mediated by central norepinephrine, which may be estimated using pupillometry. Difficulty in being able to adapt learning optimally in response to volatile environments might contribute to the decision-making difficulties seen in anxiety. Methods: We tested this hypothesis using an aversive learning task which manipulated environmental volatility. 31 (22 female, mean age 23.7 years) non-clinical participants were recruited on the basis of their trait anxiety (measured using the trait-STAI) and completed the task while pupil diameter measurements were recorded. Data were analysed by fitting a computational learning model to participant’s behavioural and eyetracking data and then testing whether the parameters of the models correlated with trait anxiety. Results: Low anxious participants matched updating of their outcome predictions to the volatility of the current environment, as predicted by a Bayesian model. High anxious individuals showed less ability to adjust updating of outcome expectancies between stable and volatile environments [p=0.02]. This was linked to reduced sensitivity of the pupil dilatory response to volatility in the high anxious participants [p=0.005]. Conclusions: These results indicate that the learning difficulties of anxious individuals may arise from altered noradrenergic responsivity to changes in environmental volatility. Financial support from ERC grant GA 260932 awarded to Sonia Bishop [1] Behrens TE et al. (2007) Nature Neuroscience 10(9).
ME04

EARLY EMOTIONAL EFFECTS OF DULOXETINE ADMINISTRATION IN HEALTHY VOLUNTEERS: PLACEBO-CONTROLLED STUDY

Bamford S, School of Psychology, Faculty of Social and Human Sciences, Univ of Southampton, Univ Dept of Psychiatry, College Keep, 4-12 Terminus Terrace, Southampton., SO143DT, s.bamford@soton.ac.uk
Pinkney V (1), Garner M (1, 2), Baldwin DS (2) (1) School of Psychology, Univ. of Southampton (2) Clinical and Experimental Sciences, Faculty of Medicine, Univ. of Southampton

Introduction: Antidepressant drugs are known to have early effects on emotion processing when administered to healthy volunteers, and emotional adverse events are often reported in the first two weeks of antidepressant treatment of patients with depressive or anxiety disorders, more commonly in younger age groups (less than 25 yrs). However the early subjective emotional effects of antidepressant administration in healthy volunteers have not been investigated extensively. This randomized double-blind placebo-controlled investigation assessed the subjective emotional effects of the serotonin-noradrenaline reuptake inhibitor (SNRI) duloxetine, when administered to healthy volunteers, within the context of an investigation of the 7.5% CO2 inhalation experimental medicine model of generalized anxiety disorder. Method: 40 healthy volunteers provided consent to participate, and were assessed at Baseline (Day 0), at Days 3, 6, 9 and 12 (by telephone), and at Follow-up (Day 14). Duloxetine was administered at a daily dosage of 30 mg mane for the first 3 days, increasing to 60 mg mane depending on tolerability. Baseline measures included the GAD-7, Positive and Negative Affect Scale (PANAS): autonomic measures were limited to heart rate and systolic and diastolic blood pressure. During telephone assessments, participants were asked to provide responses (rated 0-100) to a diary-based questionnaire assessing feelings of anxiety, nervousness, edginess, worrying, concentration, relaxation, pleasance, and contentment. A composite ‘anxiety’ score was derived from 3 diary items (nervous/anxious/edginess; worrying; inability to stop/control worries) and the corresponding 3 items on the GAD-7. Results: Two individuals did not take study medication reliably, so are excluded from further analysis. Data is reported from 19 individuals in the duloxetine group (9 men, 10 women: mean age 24.5 yrs), and 19 in the placebo group (10 men, 9 women: mean age 24.9 yrs). No adverse events were reported. Reported anxiety (mean GAD-7 score) increased more from Baseline to Day 14 with duloxetine than with placebo, but this difference was not significant; furthermore there were no significant changes between groups in change in PANAS scores. However, diary questionnaire responses indicated differences between groups: there was a strong group x time interaction for the item ‘feeling nervous, anxious or on edge’ [F(5,180) = 3.013, p = .012], with reduced anxiety in the duloxetine-administered group at Day 3, p < .05. Bivariate correlations indicate composite scores at Days 9 and 12 were the strongest predictors of GAD-7 scores at Day 14. Discussion: Short-term duloxetine administration to young healthy volunteers was not associated with reported adverse events reflecting increased nervousness, anxiety or agitation. When compared to placebo, daily duloxetine was associated with lower self-reported anxiety, nervousness and edginess after 3 days of administration. Self-report diary questionnaire responses may be more able than the GAD-7 and PANAS to detect subtle changes in anxiety with medication or placebo. Funding: MRC Experimental Medicine in Mental Health.

ME05

A SINGLE SESSION OF BILATERAL TRANSCRANIAL DIRECT CURRENT STIMULATION (tDCS) REDUCES VIGILANCE TO FEARFUL FACES: AN EXPLORATORY HEALTHY VOLUNTEERS STUDY

Ironsides M, Dept Psychiatry, Univ of Oxford, Neurosciences Bldg, Warneford Hospital, Headington, OX3 7JX, maria.ironside@psych.ox.ac.uk
O'Shea, J (1), Harmer, C (2) (1) FMRIB Centre,Univ of Oxford,Nuffield Dept of Clinical Neurosciences, John Radcliffe Hospital, Headington, Oxford, OX3 9DU (2) Neurosciences Bldg, Warneford Hospital, Headington, Oxford, OX3 7JX

Introduction: Transcranial Direct Current Stimulation (tDCS) is a neuromodulatory technique that uses weak electrical current to increase (with anodal) or decrease (with cathodal) the probability of spontaneous brain activity in the stimulated brain region via an increase/decrease in resting membrane potential. Post-stimulation effects of tDCS have been observed, lasting up to several hours after a single session. Psychopharmacological evidence suggests these after effects are NMDA receptor dependent, reflecting changes in synaptic efficacy. A growing number of studies published in the last 5 years indicate that repeated administration of pre-frontal tDCS is a potential effective treatment for depression. In this study an experimental medicine model was used to explore the effects of tDCS on emotional processing in healthy volunteers. Methods: Subjects: 60 healthy participants (aged 18-45, 30 female) were recruited using print and online advertisements. Design: A between-groups design was carried out. This involved 20 participants receiving one of two active conditions and a further 20 receiving sham stimulation. After stimulation behavioural measures of emotional perception, memory and attention/vigilance were taken using a battery of computerised tasks. Results: The results from the measures of emotional perception, emotional memory and mood questionnaires did not result in any statistically significant, valence specific group interactions (all p>.1) and were not similar to results previously found with antidepressant drug administration in healthy volunteers. The faces dot–probe task is commonly used to measure anxiety through measuring vigilance to threat. It does this by measuring reaction times when different facial expression photographs preceede a probe to which the participants respond. A repeated measures ANOVA was carried out on the dot-probe vigilance data. There was a statistically significant two-way interaction between emotion and tDCS, F(2,54) = 3.191, p=.049. The statistically significant two-way interaction between emotion and tDCS indicates that the emotional vigilance in this task varied depending on the tDCS configuration. Conclusions: These results indicate that the sham group displays an expected attentional bias towards fearful faces and away from happy faces, shown by increased vigilance for fearful faces and decreased vigilance for happy faces. This negative bias is reversed with bilateral tDCS, indicating that bilateral tDCS affects vigilance to fearful facial expressions. These results can be compared to studies of antidepressant drug action, where SSRI citalopram was found to reduce fear vigilance in healthy volunteers using a similar dot-probe task. This project forms part of a DPhil programme which is funded by the Medical Research Council.
**ME06**

**EFFECTS OF 7.5% CARBON-DIOXIDE INHALATION ON EXPLORATORY DECISION MAKING IN HEALTHY VOLUNTEERS: EVIDENCE FROM A MULTI-ARMED BANDIT TASK**

Kwong ASF, Experimental Psychology, Univ of Bristol, 12a Priory Rd, Clifton Bristol, BS8 1TU, Alex.Kwong@bristol.ac.uk

Attwood AS(1), Ludwig CJH (1), Munafò MR (1) (1) Experimental Psychology, Univ of Bristol, 12a Priory Rd, Bristol, BS8 1TU

The regulation of exploratory and exploitative decision-making is important when facing an array of options. This includes striking a balance between selecting between familiar exploitative decisions that have benefited us in the past, or new exploratory choices that may potentially give us greater gains. Whilst previous research has examined the effects of anxiety on decision-making and found that anxious decision-making tends to reflect a more risk-avoidant approach, no research has specifically examined this balance between exploratory and exploitative decision-making under conditions of anxiety. Furthermore, many studies have investigated trait anxiety rather than state anxiety, while studies that do investigate state anxiety typically induce anxiety prior to completion of the decision-making task. In order to fully understand the relationship between anxiety and decision-making, decision-making must take place under conditions of experimentally-induced elevated anxiety. Here we used the 7.5% carbon-dioxide (CO2) inhalation model to induce anxiety whilst subjects completed a decision-making task. Thirty-two healthy volunteers (50%) were recruited to take part in a single study session consisting of one air and one 7.5% CO2-enriched air inhalation (counterbalanced), during which they performed a four-armed bandit decision-making task, which presents four slot machines each with a hidden reward that is used to measure choice behaviour. Subjective measures of anxiety (Spielberger State-Trait Anxiety Inventory state sub-scale) and physiological measures (heart rate and blood pressure) were taken after each inhalation. The primary outcome was the number of exploratory or exploitative choices made during each inhalation. CO2 inhalation resulted in increased state anxiety (mean difference = 16.58, 95% CI 12.38 to 20.78, p < .001), systolic blood pressure (mean difference = 8.69, 95% CI 5.44 to 11.95, p < .001) and heart rate (mean difference = 11.91, 95% CI 8.34 to 15.47, p < .001). There were a higher percentage of exploratory choices in the CO2 condition than the air condition indicating that participants chose to explore new slot machines rather than exploit familiar ones (mean difference = 5.09, 95% CI 0.42 to 9.77, p = .034). Contrary to expectations, our results suggest that anxiety leads to more exploratory behaviour. One possibility is that attention may narrow under conditions of elevated anxiety, resulting in more exploratory behaviour and reduced exploitation of familiar choices. However, the four-armed bandit task we used does not necessarily capture risky choice behaviours. Further research is therefore required to examine if this is reflected in more ‘risky’ decision-making. Funding: No external funding

**ME07**

**EFFECTS OF DULOXETINE ADMINISTRATION ON SUBJECTIVE, AUTONOMIC AND NEUROCOGNITIVE RESPONSE TO 7.5% CARBON DIOXIDE CHALLENGE IN HEALTHY VOLUNTEERS**

Pinkney VL, Psychology, Univ of Southampton, Faculty of Social and Human Sciences, Highfield Campus University Rd, Southampton, SO171BI, vlp1v07@soton.ac.uk

Bamford S(1), Baldwin DS(2), Munafò MR(3), Garner M(1,2) (1) Psychology, Faculty of Social and Human Sciences, Univ of Southampton; (2) Clinical Neuroscience Division, Faculty of Medicine, Univ of Bristol; (3) School of Experimental Psychology, Univ of Bristol

INTRODUCTION: Inhalation of 7.5% carbon dioxide (CO2) for 20 minutes increases subjective and physiological symptoms of anxiety and impairs attention control in healthy humans. Previous studies have shown that anxiolytics (such as lorazepam and paroxetine) can attenuate the subjective (but not autonomic) anxiety response to 7.5% CO2. We examined whether the SNRI duloxetine can attenuate CO2-induced anxiety and associated deficits in attention and emotion processing. METHOD: 40 healthy volunteers were randomised to receive either a two week course of duloxetine (30mg titrated to 60mg after 3 days) or placebo. Participants subsequently completed an emotional antisaccade task in which they looked toward (prosaccade) or away (antisaccade) from negative and neutral images during inhalation of 7.5% CO2 or air. State anxiety (measured with a modified version of the GAD-7) and autonomic arousal (blood pressure, heart rate and respiration rate) were assessed before and after each inhalation. RESULTS: 7.5% CO2 significantly increased state anxiety (mean difference = 16.58, 95% CI 12.38 to 20.78, p < .001), systolic blood pressure (mean difference = 8.69, 95% CI 5.44 to 11.95, p < .001) and heart rate (mean difference = 11.91, 95% CI 8.34 to 15.47, p < .001). There were a higher percentage of exploratory choices in the CO2 condition than the air condition indicating that participants chose to explore new slot machines rather than exploit familiar ones (mean difference = 5.09, 95% CI 0.42 to 9.77, p = .034). Contrary to expectations, our results suggest that anxiety leads to more exploratory behaviour. One possibility is that attention may narrow under conditions of elevated anxiety, resulting in more exploratory behaviour and reduced exploitation of familiar choices. However, the four-armed bandit task we used does not necessarily capture risky choice behaviours. Further research is therefore required to examine if this is reflected in more ‘risky’ decision-making. Funding: No external funding

**ME08**

**REDUCED STARTLE RESPONSE AND ALTERED NEURAL ACTIVATION DURING EMOTIONAL REGULATION IN HEALTHY VOLUNTEERS AFTER SHORT-TERM DIAZEPAM TREATMENT**

Warren MB, Psychiatry, Univ of Oxford, Neurosciences Bldg, Warneford Hospital, Oxford,OX3 7JX, matthew.warren@psych.ox.ac.uk


Recent research on antidepressant drugs (e.g. selective serotonin reuptake inhibitors, SSRIs) has highlighted the importance of neuropsychological changes in producing the drugs’ clinical effects, in particular alterations in emotional processing. However, as these drugs are often effective in both depression and anxiety, it is not clear whether these changes relate to their antidepressant or anxiolytic properties. Benzodiazepines provide a
means to disentangle these effects, as they are not used to treat depression: therefore, any neuropsychological effects may be related to the drugs’ anxiolytic action. To date research into benzodiazepines has been restricted to acute doses, while little is known about neuropsychological effects after short-term treatment, which is more clinically relevant and may differ from acute effects. The aim of our study was therefore to characterise the neuropsychological effects of short-term treatment with the benzodiazepine diazepam. Thirty-six healthy volunteers received either diazepam (15mg/day) or placebo for 7 days in a double-blind study. Testing occurred on the final two days of treatment. An emotion-potentiated startle task was used, in which participants heard bursts of loud noise while viewing positive or negative pictures. Participants also underwent an fMRI scan while performing a task that required them to either maintain or regulate the emotions that they felt in response to negative pictures. The diazepam group showed a reduced startle response (amplitude of eye-blink) in the emotion-potentiated startle response, which was not specific to the valence of the picture (p < .05). In the emotional regulation task, the placebo group showed greater activation in the ventrolateral prefrontal cortex, somatosensory cortex and cerebellum while regulating their emotional response (Z > 2.3, p < .05), suggesting downregulation of activity in these areas by diazepam. The overall reduction in startle response is consistent with studies on acute doses of diazepam. It may represent an important difference in the neuropsychological effects of solely anxiolytic drugs and antidepressives: short-term antidepressant drug treatment appears to reduce blink response only to negative pictures or not at all (Harmer et al., 2004, Am. J. Psych., 161, 1256-1263). The neuroimaging data suggest that diazepam may exert its anxiolytic effects by reducing activity in areas associated with limbic control or emotional processing. It will be important to investigate whether this pattern of neural activity is different after participants take antidepressant drugs such as SSRIs. Study funded by a Medical Research Council grant.

ME09

EFFECTS OF SHORT-TERM DIAZEPAM ADMINISTRATION ON RESTING-STATE FUNCTIONAL CONNECTIVITY IN HEALTHY VOLUNTEERS: A RANDOMIZED, DOUBLE-BLIND STUDY

Pflanz CPP, Dept of Psychiatry, Univ of Oxford, Warneford Hospital, Warneford Lane, Oxford OX3 7JX, patrick.pflanz@psych.ox.ac.uk

Introduction: Benzodiazepines, such as diazepam, are anxiolytic-sedative drugs, used for the treatment of a plethora of diseases. The pharmacological mechanism of action of benzodiazepines is well understood; however, it remains unclear which neural networks and systems are involved in translating these neurochemical actions into their therapeutic effects. Therefore, the present study aimed at investigating the effects of short-term diazepam administration compared to placebo on resting-state functional connectivity in healthy adults. Resting-state fMRI has been proposed to measure intrinsic, task-independent network properties of brain organization (Fornito, A., et al., 2010, Curr Opin Psychiatry, 23(3), 239-249), thereby offering an attractive framework for studying drug effects. Methods: We used a randomized, double-blind design, in which we administered diazepam or placebo to healthy subjects (N=34) over 7-8 days (15 mg daily). 34 subjects (18 females) underwent resting-state functional magnetic resonance acquisition. Model-free data analysis was performed using independent component analysis and dual regression (Filippini, N., et al., 2009, Proc Natl Acad Sci USA, 106(17), 7209-7214). Results: Consistent with previous research 11 resting-state networks were identified. Increased connectivity in response to diazepam administration was found in the medial visual network, and middle/inferior temporal network, including the hippocampus and parahippocampal gyrus. The latter network was extended into the bilateral insula, and amygdala. Increases in functional connectivity did not correlate with anxiety scores, acquired outside the scanner. Diazepam did not cause any decreases in functional connectivity. Conclusions: Diazepam administration apparently increases functional connectivity in areas of emotional processing unconfounded of any bias by task. These increases in functional connectivity seem to be characteristic for CNS depressants and are consistent with previous research (Licata, S. C., et al., 2013, Neuroimage 70, 211-222). Converging evidence from task-based (e.g. Del-Ben, C. M., et al., 2012, J Psychopharmacol, 26(4): 443-451) and resting-state fMRI studies hint at the role of the amygdala and the insula as crucial brain regions underlying diazepam’s anxiolytic effect at the brain system level. Diazepam also enhanced functional connectivity in the medial visual system, which has not been previously reported in task-based fMRI studies. Overall, our findings indicate that resting-state fMRI has the potential to detect drug modulatory effects on the BOLD fMRI signal in large brain networks, which would have been neglected or underestimated using a certain task paradigm. The study was funded by the Medical Research Council.

ME10

EFFECTS OF TIAGABINE ON MULTIMODAL IMAGING OUTCOME MEASURES: REGRESSION TO THE MEAN OR GABAERGIC FEEDBACK?

Myers JFM, Centre for Neuropsychopharmacology, Imperial College London, Burlington Danes Bldg, Hammersmith Hospital Campus 160 Du Cane Rd London, UK, W12 0NN, j.myers@imperial.ac.uk
Evans, CJE(2), Muthukumaraswamy, S(2), Stokes, P(1), Nutt, DJ(1), Lingford-Hughes, AR(1)(1) Centre for Neuropsychopharm, Imperial College London, Burlington Danes Bldg, W12 0NN; (2) CUBRIC, School of Psychology, Cardiff Univ, Park Place, CF10 3AT

Introduction: Previous studies concerning the effects of the GABA reuptake inhibitor tiagabine have yielded interesting results and opened avenues for novel imaging methodology, informing the interpretation of GABA modulation after pharmacological or psychological challenges (Myers et al., 2012, JCBFM 32, S66; Myers et al., 2013, J Psychopharm. 27, MG07; Muthukumaraswamy et al., 2013, Neuropsychopharm. 38, 1105-1112). Three imaging studies, on separate cohorts, were conducted, using PET, MRS and MEG, each with a 15 mg oral dose of tiagabine. These studies had primary hypotheses concerning a change in outcome measure from increased synaptic GABA following uptake blockade. Specifically, using [11C] Ro15-4513 PET, we hypothesised a decrease in inverse-agonist binding to the synaptic GABAa1 receptor due to increased GABA, according to the GABA shift. Using MRS, we hypothesised an increase in concentration of GABA+ using MEGA-PRESS and with MEG, an increase in resting
gamma power. In each study a significant relationship was evident between effect size post-challenge and baseline value. Here we explore the extent and possible source of this regression. Methods: Data from each imaging study were examined for primary outcome measure at baseline and delta, the difference after tiagabine challenge. Linear regression lines were fitted to these data, for 12 (PET), 8 (MRS) and 14 (MEG) healthy volunteers.

Results: There was a significant linear regression of [11C]Ro15-4513 vs delta in the nucleus accumbens (R²=0.866, p<0.0001). In the right limbic MRS voxel, the relationship between [GABA+] at baseline and delta was also strong (R²=0.886, p<0.0005). MEG measures of high and low gamma power in the occipital lobe displayed a similar relationship between power at baseline and change in power (R²=0.730, p<0.0005; R²=0.674, p<0.0005). ROIs were chosen for high signal, though the effect was robust over the whole brain. Discussion: The influences of known synaptic feedback mechanisms to regulate GABAergic neurotransmission are consistent with the changes in measure in each study. The negative modulation of GABA on its own release through presynaptic autoreceptors has been demonstrated, as has the rapid recycling of GAT1 in a fashion similar to the neurotransmitter.

Therefore, it is possible that, with high baseline GABA, transient blockade of uptake results in an overall decrease in GABA, as opposed to the expected increases observed when baseline GABA is low. This might explain unexpected drug effects in each study, though we cannot reject regression to the mean without further experimentation. Studies were funded by an MRC programme grant.

ME11

DIFFERENCES BETWEEN MAGNETOEENCEPHALOGRAPHIC (MEG) SPECTRAL PROFILES OF DRUGS ACTING ON GABA AT SYNAPTIC AND EXTRASYNAPTIC SITES: A STUDY IN HEALTHY VOLUNTEERS

Wilson SJ, Neuropsychopharmacology, Div of Brain Sciences, Imperial College London, Burlington Danes Bldg, Hammersmith Campus, DuCane Rd, London, W12 0NN, sue.wilson@imperial.ac.uk
Nutt,DJ (1) Lingford-Hughes,AR (1) Myers,FJM (1) Papadopoulos, A (2) Muthukumarswamy, SD (3) (1) Div of Brain Sciences, Centre for Neuropsychopharmacology, Imperial College London (2) Psychopharmacology Unit, School of Social and Community Medicine, Univ of Bristol (3) CUBRIC, School of Psychology, Cardiff Univ

In this study we compare the effects on resting MEG spectra of three GABAergic drugs with highly specific and distinct mechanisms of action. These were the benzodiazepine receptor agonist zolpidem, the delta sub-unit selective agonist gadoxadol (also known as THIP) and the GABA reuptake inhibitor tiagabine. Effects on the waking EEG of benzodiazepines and Z drugs are well-documented but effects of the drugs which affect GABA differently, for example by effects on extrasynaptic receptors, or by inhibition of reuptake, have not been studied in man. Effects on sleep studies in humans however show marked differences between these drugs and therefore it would be interesting to compare their effects on the waking state. These were two randomised, single-blind, placebo-controlled, crossover studies in healthy volunteers, one a comparison in 10 males of zolpidem 10mg, gadoxadol 15mg and placebo , and the other a comparison of tiagabine 16mg and placebo in 14 participants, one female. Whole head MEG recordings were made using a 275-channel radial gradiometer system sampled at 1200 Hz. After artefact rejection, data was converted to planar gradient configuration, and frequency analysis conducted using Hanning windowed fast Fourier transformers. Planar directions were combined to give local maxima under the sensors. Individual spectra were divided into the following frequency bands, delta (1 - 4 Hz), theta (4- 8 Hz), alpha (8 - 13 Hz), beta (13 - 30 Hz), low gamma (30 - 50 Hz) and high gamma (50 - 100 Hz). Baseline spectra were subtracted from each post-intervention spectra and then differences between intervention and placebo compared by permutation testing at each post intervention time-point. We present statistical maps of the changes. The findings for zolpidem were as previously reported in EEG studies, with significant increases in beta frequencies and reduction in alpha frequency power; for gadoxadol and tiagabine there were significant increases in power at all frequencies up to beta. Thus the enhancement of tonic inhibition by via extrasynaptic receptors by gadoxadol gives rise to a very different MEG signature from the synaptic action of zolpidem. Tiagabine theoretically can affect both types of receptor, the first by blocking uptake in the synapse and therefore it allowing more post-synaptic enhancement of tonic inhibition by via extrasynaptic receptors by gaboxadol gives rise to a very different MEG signature from the synaptic action of zolpidem. Further studies are needed to explore the extent of these differences.

ME12

INCREASED CERTAINTY SEEKING (CHECKING) BEHAVIOUR IN A PUNISHED VERSION OF THE OBSERVING RESPONSE TASK IN RATS: A TRANSLATIONAL MODEL OF COMPULSIVE CHECKING IN OBSESSIVE-COMPULSIVE DISORDER (OCD)

Eagle DM. Dept of Psychology and BCNI, Univ of Cambridge, Downing Site, Cambridge, CB2 3EB, de102@cam.ac.uk
Atherton TG(1), China Z(1), Lau JYNL(1), Sherwood T(1), Yuan J-M(1), Milton AL(1), Mar AC(1), Urcelay GP (1), Morein S(1), Robbins TW(1).
(1) Dept of Psychology and BCNI, Downing Site, Cambridge, CB2 3EB

Introduction: Obsessive-compulsive disorder (OCD) is a debilitating condition (prevalence 1-3%), with compulsive checking one of the more commonly-reported symptoms. Compulsive checking routines relate to security/information/certainty-seeking (e.g., checking doors are locked), often at the expense of normal function. These routines are often performed to avoid perceived negative consequences or punishment. Methods: We trained 18 male Listnor-hooded rats (weight 240±20g) on the observing response task. Rats pressed two levers on the front wall of an operant conditioning chamber in order to earn rewards on a variable ratio schedule (VR10-20) of lever presses. At any one time, only one lever was ‘active’ giving food reward. The position of the active/inactive levers switched on a pre-determined schedule. However, a press on a third lever, the observing lever, located at the back of the chamber, gave information about the location of the active lever, in the form of a light above the active lever for 15 seconds. In previous studies (Eagle DM et al. Behavioural Brain Research 264:207-29), and during baseline training, the ‘inactive’ lever gave no consequence. During the experimental test phase, rats received progressively-increasing intensity of foot-shock (0.1, 0.2, 0.3, 0.4, 0.5 mA, max 30 shocks/session, schedule VR10-20 inactive presses) for responses on the inactive lever. Results: Checking responses, in the form
of number of informative observing lever presses (OLPs) and number of non-informative perseverative extra observing lever presses (EOLPs) increased with increasing intensity of foot-shock [repeated-measures ANOVA: OLPs F(3.58)=19.53, p<0.001, partial-η2=0.54; EOLPs F(3.46)=7.35, p<0.001, partial-η2=0.30]; foot-shock intensity of 0.3mA and above induced significantly higher OLPs [all F(1,17)>9.0, p<0.01; partial-η2>0.35] and foot-shock intensity of 0.4mA and above induced higher EOLPs [all F(1,17)=8.56, p=0.01, partial-η2=0.34]. Rats changed their behaviour such that fewer shocks were self-administered at higher intensity foot-shock [F(3,56)=53.61, p<0.001, partial-η2=0.76]. Conclusions: Rats increased checking-like behaviours on the observing response task as the intensity of possible punishment for incorrect responses increased. Functional OLPs were more sensitive to punishment than non-functional EOLPs. Rats consequently changed their behaviours to reduce the frequency of punishments during a session. This model has excellent translational potential to investigate compulsive checking behaviour in OCD. Funding: This study was supported by a Wellcome Trust programme grant (089589/Z/09/Z) awarded to TW Robbins, BJ Everitt, BJ Sahakian AC Roberts and JW Dalley and carried out within the University of Cambridge Behavioural and Clinical Neuroscience Institute, supported by a joint award from the Medical Research Council and Wellcome Trust.

ME13
THE EFFECTS OF PERCEIVED THREAT ON CHECKING BEHAVIOUR IN RATS AS A POTENTIAL MODEL OF OBSESSIVE-COMPULSIVE DISORDER
Lau JYN, Dept of Psychology, Univ of Cambridge, Downing Site Cambridge, CB2 3B, jynl2@cam.ac.uk
Atherton TG(1), Mar AC(1), Urcelay GP (1), Morein S(I), Milton AL(1), Eagle DM(1), Robbins TW(1).

Introduction: Obsessive-compulsive disorder (OCD) is a highly complex disorder with various symptoms, of which one of the most common is compulsive checking. It is thought that this checking behaviour is primarily due to a desire for certainty, or as an overreaction to a perceived threat. This study aimed to determine the relationship between the memory of perceived threat and checking behaviour in a newly developed model of OCD checking, the observing response task (ORT), to examine the model’s predictive validity. Methods: We trained 18 male Lister-hooded rats on the observing response task, ORT (Shock-conditioned n=9, no-shock control n=9). In this task, rats pressed two levers on the front wall of an operant conditioning chamber in order to earn rewards on a variable ratio schedule (VR10-20) of lever presses. At any one time, only one lever was ‘active’ giving food reward. The position of the active and inactive levers switched on a pre-determined schedule. However, a press on a third lever, an observing lever press (OLP), located at the back of the chamber, gave information about the location of the active lever, in the form of a light above the active lever (for 15 seconds). Perceived threat was achieved by transferring contextual cues associated with fear conditioning into the ORT. Following baseline performance in the ORT, rats received contextual fear conditioning (2 minutes exposure to context [visual and olfactory cues], 1s x 0.5mA foot-shock (or no shock in the control group), 1 further minute exposure to context). On the following day, rats were retested in the ORT, in the context associated with fear conditioning. Later that day, rats were assessed for freezing behaviour to the context. Results: There was little direct effect of shock-conditioning training on ORT task performance, and no effects on checking behaviour (shock-group by pre-post conditioning, all F<2.5, n.s.). However, within the shock-conditioned group, there was a strong correlation between change in freezing following fear-conditioning, and change in checking (OLPs) during the ORT in the presence of the fear-conditioning context compared to their ORT measures at baseline (n=9, r=0.71, p=0.05), suggesting a link between high-level checking and the extent to which a context is associated with potential threat. Conclusions: This study shows that there is a possible link between perceived threat and checking behaviour. This model has excellent translational potential to investigate the role of perceived threat during the development of excessive checking behaviour in OCD.

ME14
REFINED INTRAPERITONEAL DOSING METHOD FOR RATS REDUCES STRESS
Robinson ESJ, School of Physiology and Pharmacology, Univ of Bristol, Medical Sciences Bldg, University Walk, Bristol, UK, BS8 1TD, pmesjr@brs.ac.uk

The majority of preclinical studies in psychopharmacology involve the administration of drugs. In rodents, one of the most widely used routes of administration of substances is intraperitoneal. This method requires the animal to be restrained and can result in struggling and vocalisation suggesting increased levels of stress. As part of our ongoing work to refine the procedures used in our research, we have investigated whether a modified, minimal restraint technique is associated with reduced stress. The study used four separate cohorts of rats of different ages, strain and level of prior handling (~250g Wistar n=6, 500g+ Wistar n=5, 500g+ Ex breeding Wistar n=5, 500g+ handled Lister-hooded n=8). Half of each cohort was dosed using a conventional restrained technique whilst the other half were dosed using a minimal restrained method. The modified dosing method involved gentle cupping the animals against the body and tilting slightly back to expose the belly. The abdomen was kept in a relaxed position. Observations of vocalisation, struggling and faecal counts were made by an independent observer. In one cohort, post-mortem cortisol levels were also measured. In a separate cohort, the rodent affective bias test (Stuart et al., 2013, Neuropsychopharmacology 38:1625-35) was used to test if the conventional dosing methods induced a more negative affective state. The ABT was carried out as previously described but with the different dosing method used on separate days prior to two independent learning experiences (finding a food reward in a specific digging medium). A preference test was then used to provide an indication of dosing-induced affective state. Looking at all groups together, the modified dosing technique was associated with reduced vocalisation, struggling and faecal counts. In the well handled animals, the differences in vocalisation and struggling scores were particularly marked. Indication of dosing and vocalisation scores were reduced in all groups except the 500g+ Wistar. Faecal counts were not reduced in any single cohort but when the data was pooled an overall reduction was seen. Cortisol levels were lower in the animals dosed using the modified method. In the affective bias test, animals made more choices for the experience encountered results suggested animals dosed using the conventional method were in a more negative affective state than the animals dosed using the modified method. Together, these data suggest this modified method of intraperitoneal dosing is associated with better welfare. Animals showed less aversion to dosing and a reduced stress response with the modified method. Funding provided by: BBSRC, MRC and Wellcome Trust.
**MF01**

**DISSOCIATIVE EFFECTS OF PRAMIPEXOLE ON PROBABILITY DISCOUNTING AND MOTOR FUNCTION IN A RAT MODEL OF PARKINSON’S DISEASE**

Tedford SE, Pharmacology, RUSH Univ, 1735 West Harrison St, Chicago, IL, 60612, 60612, Setedford@gmail.com

Holtz NA (1,3), Persons AL (1,3), Napier TC (1,2,3) (1) Dept of Pharmacology, RUSH Univ, Chicago, IL, USA. (2) Dept of Psychiatry, RUSH Univ, Chicago, IL, USA. (3) Center for Compulsive Behavior and Addiction, Rush Univ, Chicago, IL, USA.

Introduction: Parkinson’s disease is characterized by loss of dopamine (DA) in the nigrostriatal pathway resulting in distinctive motor disturbances (e.g., postural instability, bradykinesia, resting tremor). These deficits are commonly treated with DA agonists, including pramipexole (PPX).

However, in some PD patients, PPX therapy is associated with the development of impulse control disorders (ICDs), such as pathological gambling. To investigate the relationship between PPX-induced motor improvement and ICD development in PD, we studied the effects of a therapeutically relevant dose of PPX, i.e., one that improved postural instability in a rat model of PD on risk-taking behavior, an aspect of problem gambling.

Methods: The forelimb adjustment step test was used to assess postural instability in rats throughout the experiment. To model early stage PD, the dopaminergic toxin 6-OHDA was injected bilaterally into the dorsolateral striatum (DLS; rat homolog of human putamen) of anesthetized rats. At the same time, a stimulating electrode was implanted within the lateral hypothalamus. Intracranial self-stimulation (ICSS) was subsequently used as the positive reinforcer to measure risk-taking behavior in a probability discounting task. During this operant task, rats were able to select between a small stimulation reinforcer presented immediately after lever pressing and a large stimulation reinforcer presented after varying probabilities. After stable baseline behavior was determined, rats were subcutaneously implanted with an osmotic mini-pump that delivered 0.3 mg/kg/day PPX for 14 days.

Results: 6-OHDA-induced lesions of the DLS significantly decreased adjustment stepping (two-way rmANOVA with post hoc Newman-Keuls, *p<0.01). Following implantation of the PPX minipump, rats showed robust improvements in stepping behavior that stabilized at pre lesion levels and lasted throughout PPX treatment (one-way rmANOVA with post hoc Dunnetts; *p<0.01). Upon PPX removal, stepping deficits returned within 8 hr (one-way rmANOVA with post hoc Dunnetts; *p<0.01). However, PPX induced only small transient increases in probability discounting. This outcome contrasted our published work showing that probability discounting is significantly and persistently enhanced in this model with much higher doses of PPX (4 mg/kg/day) (Rokosik and Napier, NPP, 2012). Conclusions: These data reveal that 0.3 mg/kg PPX provided robust improvement in motor stepping deficits associated with an early-stage model of PD, but had only slight transient effects on risk-taking behavior. These findings are in keeping with the immediate motor benefits seen in PD patients following PPX treatment, and that patients typically do not exhibit ICDs until medication has been taken over extended periods of time or with dose escalation. Acknowledgements: USPHSGs #NS074014 and #DA033121.

**MF02**

**NEUROPROTECTIVE PROPERTIES OF FK866 IN IN VIVO MODELS OF NEURODEGENERATION**

Othman OA, School of Life Sciences, Univ of Nottingham, Medical School, Queens Medical Centre, Derby Rd, Nottingham, England, UK, NG7 2UH, mbxoo@nottingham.ac.uk

Conforti L(1), Pardon M-C(1) (1) School of Life Sciences, Univ of Nottingham Medical School, Queens Medical Centre, Derby Rd, Nottingham, England, UK, NG7 2UH

Introduction: Several studies suggest that axonal degeneration is an early event in a variety of neurodegenerative diseases including Huntington’s disease (HD) and Alzheimer’s disease (AD), where it correlates with symptom onset and progression. The importance of nicotinamide adenine dinucleotide (NAD) synthesis pathway in the protection of axons following acute injury and in experimental models of neurodegeneration has been demonstrated. We have found that FK866 – a highly specific inhibitor of a key enzyme in NAD biosynthesis which catalyses the formation of the NAD precursor nicotinamide mononucleotide (NMN) – reduces axonal degeneration in in vitro models of HD and AD. Here, we tested the possibility that FK866 could also improve behavioural symptoms in in vivo models of these neurodegenerative diseases, and compared that to the well-defined neuroprotective effects of the N-methyl-D-aspartate receptor (NMDAR) antagonist memantine. Methods: Six month old Q140 mice, a knock-in mouse model of HD, APPswe/PS1ΔE9 mice, a transgenic mouse model of AD, and their nontransgenic littermates (n=12/group) were administered FK866 (15 mg/kg/day i.p.) in combination with nicotinic acid – to salvage NAD biosynthesis while still inhibiting NMN with FK866 - (50 mg/kg/day in drinking water), or memantine (20 mg/kg/day i.p.), or vehicle for 3 weeks. The effect of treatments on locomotor activity, spatial learning, sensorimotor gating and anxiety-related behaviour were assessed using rotarod, open field, elevated plus maze, spontaneous alternation, and prepulse inhibition (PPI) tests. Results: There was no significant effect of FK866/nicotinic acid combination and memantine treatments on spatial learning. Interestingly however, the FK866/nicotinic acid combination significantly reduced APPswe/PS1ΔE9 mice hyperactivity (p<0.001) to levels similar to those of their nontransgenic vehicle-treated littermates. Memantine significantly restored the reduction in locomotor activity of Q140 mice (p<0.05) to levels similar to their nontransgenic vehicle-treated littermates. In addition, memantine significantly increased PPI% and PPI peak startle amplitude which were reduced in APPswe/PS1ΔE9 mice (p<0.05), to levels similar to their nontransgenic vehicle-treated littermates. Conclusions: These data demonstrate that modulation of NAD synthesis pathway with FK866/nicotinic acid combination and blocking NMDAR with memantine significantly improved the locomotor activity of APPswe/PS1ΔE9 mice and Q140 mice respectively, with no effect on their spatial learning. Moreover, our data revealed that memantine significantly improved the sensorimotor gating abnormalities of APPswe/PS1ΔE9 mice as measured by PPI test. We conclude that modulation of NAD synthesis pathway with FK866/nicotinic acid combination not only reduces the axonal degeneration in vitro, but also restores some of behavioral abnormalities in in vivo models of neurodegeneration. My PhD project is sponsored by The Higher Committee for Education Development in Iraq (HCED-IRAQ).
MF03

NEUROINFLAMMATION INDUCED BY LIPOPOLYSACCHARIDES DOES NOT SIGNIFICANTLY IMPAIR CONTEXTUAL FEAR CONDITIONING BEHAVIOUR IN THE APPSWE/PS1ΔE9 MODEL OF ALZHEIMER’S DISEASE

Barron M, School of Life Sciences, Univ of Nottingham, Room E175, Medical School, Queen’s Medical Center, Nottingham, NG7 2UH, mbxmrb@nottingham.ac.uk
Agostini A(1), Faas H(2), Pardon MC(1) (1) School of Life Sciences, Univ. of Nottingham, Queens Medical Center, Nottingham, NG7 2UH (2) School of Clinical Sciences, Univ. of Nottingham, Queens Medical Center, Nottingham, NG7 2UH

Neuroinflammation and microglial activation are key features of Alzheimer’s disease (AD) but their contribution to disease progression is poorly understood. We assessed the effect of lipopolysaccharide (LPS), an immune challenge and selective agonist of toll-like receptor 4, exclusively expressed on microglia in learning and memory performance in a contextual fear conditioning paradigm using a genetic mouse model of AD. 4-month-old female APPswe/PS1ΔE9 and wild-type littermates (n=9-11/group) were assessed in a contextual fear conditioning pre-exposure protocol, specifically chosen for the animals to recover from the confounding effects of sickness syndrome. On day 1 the mice were pre-exposed to the context, a box with stainless steel panel sides and stainless steel grid flooring, for 5 minutes followed by 5 repeats of 40s in/out of context. Immediately after the pre-exposure, an I.V. injection of LPS (100µg/kg) or vehicle (PBS) was administered. Conditioning was performed on day 3 in the same context involving an immediate shock (0.4mA, 1s), followed by a shock each minute for 9 minutes (10 shocks in total). 3 minute retention and extinction trials were held in the same context on day 4 and 5 respectively. Immobility was the measure for learning and memory of contextual fear. The data was analysed with a two-way ANOVA (two-way ANOVA with repeated measures for the conditioning trial) followed Tukey’s post hoc analysis where appropriate. Their brains were collected for assessment of glial activation (GFAP and IBA1 immunostaining). LPS treated mice exhibited classical sickness symptoms but recovered by the conditioning trial. APPswe/PS1ΔE9 mice did not differ from wild-type littermates during the pre-exposure trial. A trend for an impairment in acquisition of contextual fear was observed in LPS treated mice (p=0.083). Significant impairments in immobility during the retention trial were exhibited in APPswe/PS1ΔE9 mice (p<0.05), although no significant effect on the extinction index was observed. There was no significant effect of LPS throughout the study. Glial activation assessment is ongoing. Although we report no LPS-induced deficit, the paradigm is valuable in assessing contextual fear with inflammatory challenges without being confounded by the associated sickness effects, wherein APPswe/PS1ΔE9 mice demonstrate impairments. However, improvement to our paradigm could be made in that learning might have occurred during conditioning due to too numerous shocks and/or recovery form neuroinflammatory changes to the brain. Thus, the animal may not rely on learning from the pre-exposure session. The study offers an interesting technique to assess contextual fear conditioning in immune challenge studies. Sources of financial sponsorship: MRC industrial CASE studentship with Eisai Ltd.

MF04

A TIME-COURSE ANALYSIS OF LIPOPOLYSACCHARIDE-MEDIATED NEUROINFLAMMATION IN APPSWE/PS1ΔE9 MICE

Parhizkar S, Life Sciences, Univ of Nottingham, Medical School, Queen’s Medical Centre, Nottingham, NG7 2UH, parhizkar.samira@gmail.com
Knapp S(2), Pardon M-C(2) (2) The Univ of Nottingham Medical School, Queen’s Medical Centre Nottingham NG7 2UH

For many years, the prevailing view of neuroinflammation in AD has been regarded as an on-off phenomenon that contributes to the cytotoxicity of AD lesions and therefore contributes to the neurodegeneration in AD. It is only within the recent decade that neuroinflammation has come to the forefront of AD research. Toll-like 4 (TLR4) is activated by lipopolysaccharide (LPS), and TLR4-LPS interaction is well known to induce an innate immune response, triggering sickness behaviour observed in chronic neurodegeneration. The effects of TLR4 activation on brain function have not been widely studied in models of AD. Here, we show for the first time that acute systemic inflammation with TLR4 ligand LPS induces sickness syndrome in mice early in the progression of disease in a model of AD. Duration of sickness behaviour pattern induced by systemic LPS challenge was investigated in APPswe/PS1ΔE9 and C57Bl/6 mice, with an additional focus on potential sex-dependent differences. Systemic inflammation was induced in mice using LPS at 100µg/kg to mimic aspects of bacterial infection. Changes in core body temperature, locomotor activity and spatial working memory were assessed 1 and 2 days after the challenge using Y-maze spontaneous alternation and real-time measurements in free-ranging animals with radiotelemetry. The effect of LPS in all 4-month-old mice was assessed using repeated measures ANOVA with Tukey’s post-hoc analysis for multiple comparisons. Sub-pyrogenic inflammation induced sickness behaviour, decreasing locomotor activity, body weight and caused photic-like phase delay (8h) in body temperature in a gender- and genotype-specific pattern. Male transgenics (n=4) and wildtypes (n=7) as well as female wildtypes (n=4) displayed a biphasic temperature response up to 36h; female APPswe/PS1ΔE9 mice (n=4) were markedly insensitive to the physiological responses to LPS. For the locomotor activity, no significant effect of interaction between gender x genotype x treatment (F(3,16)=0.793, p=0.516) was observed. Similarly, no statistical significance was observed for temperature (F(3,16)=1.987, p=0.157). These responses were not significantly blunted upon a second challenge 2 weeks later. No changes in working memory were observed and none of the groups reached statistical significance (F(4,48)=0.54, p=0.705). These findings demonstrate CNS effects of peripheral TLR4 stimulation and highlight the importance of addressing neuro-immune interactions involved in AD. Changes in circadian activity patterns such as decreased rhythm amplitude, phase delays are significant predictors of subsequent AD or mild cognitive impairment suggesting that compromised rhythms might be a preclinical phenomenon. We wish to gratefully acknowledge BAP for their generous financial support of this work.
STAGES OF ALZHEIMER’S DISEASE: ICV ADMINISTRATION OF SOLUBLE AMYLOID-β OLIGOMERS IN THE RAT

INVESTIGATING COGNITIVE DEFICITS AND NEURONAL MARKERS IN AN ANIMAL MODEL OF RELEVANCE TO THE EARLY STAGES OF ALZHEIMER’S DISEASE: ICV ADMINISTRATION OF SOLUBLE AMYLOID-B OLIGOMERS IN THE RAT

Cognitive deficits linked to hippocampal dysfunction have been identified using touchscreen based tasks in patients with Alzheimer’s disease. In order to facilitate translational research touchscreen-equipped operant chambers are increasingly used to evaluate aspects of cognition in rodent models of neurodegenerative disorders. The aim of this study was to investigate the acquisition of spatial (SD) and visual discriminations (VD) in aged mice with aggressive Aβ plaque pathology. TASTPM mice harbour both the Swedish double mutation and human presenilin-1 (M146V) mutation. Learning was assessed in modified modular test chambers (Med Associates) that had a touch-sensitive computer screen directly opposite the magazine. This was masked with a black Perspex sheet into which two (VD) or four (SD) response location windows had been cut. Following habituation, 21 month old TASTPM (n=10) and age matched WT controls (n=17) were trained to nose poke the touchscreen for a pellet reward. They were then tested sequentially for SD (16 sessions) followed by VD acquisition (6 sessions). The SD stimuli comprised identical images (white squares) in two of four locations. Correct responses in location 1 or 4 were rewarded and incorrect responses in locations 2 or 3 were not. The VD stimuli comprised circles or horizontal lines and were presented simultaneously. The location of the correct and incorrect stimuli was randomly presented. The correct/incorrect stimuli (lines vs. circles) was counterbalanced. Data was analysed by ANOVA. The performance of TASTPM mice on the spatial discrimination task was significantly worse compared to WT controls as measured by % correct (F1,25=15.3; p<0.001), despite a lower % omissions (F1,25=10.6; p<0.01). There was no difference in the number of trials completed per session. TASTPM mice exhibited slightly shorter response latencies (F1,25=8.0; p<0.01) and longer magazine latencies (F1,24=6.7; p<0.05), although both of these differences were minimal. In contrast, there were no differences between TASTPM and WT mice in a simple visual discrimination task. In conclusion the data show that aged female TASTPM mice are significantly impaired in the acquisition of a spatial discrimination. The data suggest that this is not due to a visual impairment or differences in activity and any changes in motivation are minimal. Thus the data indicates that TASTPM mice are cognitively impaired in a spatial discrimination task, potentially indicative of hippocampal dysfunction as a result of Aβ pathology. This work was supported by the PharmaCog, Innovative Medicine Initiative under Grant Agreement n°115009.

MF06

INVESTIGATING COGNITIVE DEFICITS AND NEURONAL MARKERS IN AN ANIMAL MODEL OF RELEVANCE TO THE EARLY STAGES OF ALZHEIMER’S DISEASE: ICV ADMINISTRATION OF SOLUBLE AMYLOID-B OLIGOMERS IN THE RAT

Introduction: With current treatments for Alzheimer’s disease (AD) only providing temporary symptomatic benefits and an ageing population, disease modifying drugs are urgently required. This approach relies on improved understanding of the early pathophysiology of AD. A new hypothesis has emerged, in which early memory loss is considered a synapse failure caused by soluble Amyloid-β (Aβ) oligomers. These small soluble Aβ oligomers, which precede the formation of larger fibrillar assemblies, may be the main cause of early AD pathologies. Previous studies have reported decreased N-acetylaspartate (NAA), a marker of neuronal loss, in AD patients while studies in patients during the first symptomatic stages of the disease vary between physiological and low levels. Thus NAA has been suggested as a potential diagnostic marker for the conversion from mild cognitive impairment to dementia. The aim of the current study was to determine whether the cognitive deficits observed following acute intracerebroventricular (ICV) administration of soluble Aβ oligomers in the rat was concomitant with changes in the levels of NAA in the brain.

Methods: Adult female hooded Lister rats (230±20g) received ICV administration of vehicle or soluble Aβ42 oligomers (n=10/group). Animals were tested in the novel object recognition (NOR) paradigm, to assess recognition memory, 14 days following Aβ administration. Following behavioural experiments brains were removed and analysed for levels of NAA in various brain regions using HPLC. Data from vehicle and Aβ groups were analysed in SPSS using a one-way Anova. Results: In the NOR paradigm, vehicle treated rats spent significantly (p<0.001) more time exploring the novel compared to the familiar object, an effect that was abolished in Aβ treated animals. We found no significant differences in levels of NAA between vehicle and Aβ treated animals in any region investigated (frontal cortex, prefrontal cortex, striatum, dorsal and ventral hippocampus and temporal cortex). Conclusion: Findings from the present study suggest that acute ICV administration of soluble Aβ oligomers causes robust cognitive deficits without causing neuronal loss. Using a similar treatment regime, we have previously demonstrated specific deficits in synaptic markers (deficits in both pre- (SNAP25) and post-synaptic (PSD95) markers in the prefrontal cortex) and cognitive function. Taken together the results suggest that acute ICV administration of soluble Aβ oligomers may be a useful model to study the early mechanisms involved in AD and may provide us with a platform for testing novel therapeutic approaches that target the early underlying synaptic pathology. This project is funded as a Ph.D. by the University of Manchester.
MF07
INSIGHTS FROM APATHY AND IMPULSIVITY IN THE ELDERLY FOR ADVANCES IN NEURODEGENERATIVE DISORDERS

Wehmann E, Clinical Neuroscience, Univ of Cambridge, Herchel Smith Bldg, Forvie Site, Robinson Way, Cambridge, CB2 0ZS, ew426@cam.ac.uk
Coyle-Gilchrist, I(1), Rowe, JB(1) (1) Herchel Smith Bldg, Forvie Site, Robinson Way, Cambridge, CB2 0ZS

Apathy and Impulsivity are common in neurological disorders, such as Alzheimer’s disease, Frontotemporal dementia, or Parkinson’s disease (Levy, M. L. et al., 1998, Neuropsychiatry and Clinical Neurosciences, 10, 314-319). They often coexist in clinical disorders and are distressing for carers (Leiknes, I. et al., Neuropsychology, 2013, 7, 255-283), and are associated with faster cognitive and functional decline (Starkstein, S.E. et al., 2006, JNNP, 77, 8-11). In preparation for new treatments of apathy, without exacerbating impulsivity, we investigated performance of healthy participants on a battery of apathy and impulsivity tests. 30 healthy participants (15 male, mean age 68), undertook questionnaires (Apathy Evaluation Scale (AES), Barratt Impulsiveness Scale (BIS), Cambridge Behavioural Inventory (CBI), Motivation and Energy Inventory (MEI), Beck Depression Inventory (BDI), Snaith-Hamilton Pleasure Scale (SHAPS), SF36, Addenbrooke’s Cognitive Examination Revised (ACER), Parkinson’s Disease Sleep Scale (PDSS), Obsessive-Compulsive Inventory (OCIR) Kirby delay discounting task), and computerized cognitive tasks (Information Sampling Task (IST), Cued Reinforcement Reaction Time Task, Stop-Signal Task (SST), NoGo), an oculomotor version of NoGo, structural and functional MRI and 7-day actiometry. We present the initial behavioural analysis. Performances corresponded with previous studies of older adults including the AES, mean=25(5.2), and BIS, mean=57(7.7) (Marin, R.S. et al., 1991, Psychiatry Research, 38, 143-162; Stanford, M.S. et al., 2009, Personality and Differences, 47, 385-395). Total AES scores correlated significantly (p<0.01) with partner observations of behaviour (CBI), anhedonia (SHAPS), motivation/energy (MEI), and (p<0.05) depression (BDI), obsessive-compulsive behaviour (OCIR). AES was higher in men (p<0.05). AES did not correlate with sleep symptoms (PDSS), global health (SF36), cognition (ACER), or age. AES subscores revealed that AES-cognition and AES-behaviour, but not AES-emotion correlated with MEI (p<0.01); AES-cognition correlated with depression (P<0.05), while AES-cognition and AES-behaviour correlated with anhedonia (P<0.01). AES did not correlate with direct behavioural measures of impulsivity (GoNoGo, SST, IST), or Kirby. However, AES-cognition correlated (P<0.05) with oculomotor impulsivity (commission error). Principal component analysis and Canonical variate analysis may be more effective than multiple pairwise correlations at revealing the relations between apathy and impulsivity across self-report and objective physiological measures. Our data provide insights into the complex relations between apathy and impulsivity, relevant for future studies of neurological and neuropsychiatric disorders. Understanding how these constructs relate to subjective and objective measures is important for translational models, as well as interventional studies with new pharmacological treatments. This study was supported by the WellcomeTrust, the MRC Cognition and Brain Sciences Unit, and the German National Academic Foundation.

MF08
PRESCRIBING OF ANTI-DEMENTIA DRUGS IN THE UK

Barnes TRE, Centre for Mental Health, Imperial College , London, W6 8LN t.r.barnes@imperial.ac.uk
Chee S(2), Paton C(1,2) 1. Centre for Mental Health, Imperial College, London W6 8LN 2. CCQI, Royal College of Psychiatrists, London E1 8BB

Effective pharmacological therapy for dementia started in the mid-1990s with the introduction of the acetylcholinesterase inhibitors (AChE inhibitors) and more recently the NMDA partial agonist, memantine. Prescribing practice with these anti-dementia drugs was assessed in a national clinical audit in 2013, as part of a POMH-UK quality improvement programme. A customised report including benchmarked data reflecting clinical performance against best practice standards was subsequently sent to each of the 54 mental health Trusts that participated, to prompt reflection by clinicians on their practice and stimulate action plans to tackle areas where performance fell short. Data were submitted on 9,180 patients with dementia, 6,286 (68.5%) of whom were prescribed an anti-dementia drug. Donepezil was by far the most commonly prescribed AChE inhibitor. Multivariable analysis revealed that the variables significantly associated with being prescribed an anti-dementia drug included living at home (with or without a carer), being in the 66-75 age group, female gender and White ethnicity. Both severity and sub-type of dementia were also significantly associated with prescription of anti-dementia medication; these drugs were most commonly prescribed for patients with Alzheimer’s, followed by mixed dementia and Parkinson’s disease/Lewy body dementia, and for patients with dementia of moderate severity rather than mild or severe illness. Memantine is recommended, by NICE, within its licensed indication as an option for severe Alzheimer’s disease or for people with moderate Alzheimer’s disease who are intolerant of or have a contraindication to AChE inhibitors. The audit data suggested that the relatively small proportion of patients with severe dementia in the audit sample were much more likely to be prescribed memantine than an AChE inhibitor, at least within the first year of anti-dementia drug treatment. However, prescription of memantine was not limited to moderate to severe dementia, perhaps partly reflecting intolerance of AChE inhibitors in a small proportion of patients with mild dementia. Further, although dementia may become more severe over time, the findings suggested that medication is unlikely to be switched from an AChE inhibitor to memantine. Practice with respect to continuing monitoring of therapeutic response and tolerability was relatively good. For example, of the subsample of patients who had been maintained on anti-dementia medication for 7-12 months (n=927), 91% had received a follow-up review in the 6 months after anti-dementia medication was initiated, with the majority having a formal or informal global, functional, behavioural and cognitive assessment, in line with best practice recommendations. POMH-UK is supported solely by subscription from member Trusts and other healthcare organisations.
MG01
THE EFFECT OF REPEATED COGNITIVE TESTING ON COGNITIVE PERFORMANCE IN PATIENTS WITH CHRONIC FATIGUE SYNDROME
Cheeta S, Psychology, Brunel Univ, Uxbridge, Middlesex, UB8 3PH, survjit.cheeta@brunel.ac.uk
Shneerson JM (1), Smith IE (1), File SE (2) (1) Respiratory Support and Sleep Centre, Papworth Hospital, Cambridge, UK (2) Emeritus Professor of Psychopharmacology, King’s College London, London UK

Background: CFS patients often report difficulties with cognitive functioning as the most debilitating aspect of their illness. Furthermore, they also report a worsening of these symptoms during the day in their everyday lives, although objective data validating this are lacking. Methods: In order to determine whether cognitive deficits would emerge in CFS patients as a result of a long day of testing, 14 patients satisfying standard diagnostic criteria for CFS, and 14 age, gender and IQ matched controls were tested repeatedly on subjective measures of sleepiness and fatigue and on a range of objective cognitive abilities. Results: There was clear evidence from the subjective ratings that all participants felt more sleepy and fatigued in the second test session and in the CFS group there was evidence for deterioration in performance in tests of memory, attention and verbal fluency. However, despite feelings of increased sleepiness and tiredness in the afternoon testing session, improvements in performance i.e. practise effects were evident in both groups on several of the cognitive measures in the second testing session. Conclusions: We have evidence to support our hypothesis that the performance of CFS patients deteriorates on a second testing session, due to a long day of testing and increased fatigue. However, the improvements in cognitive testing seen in CFS patients with repeated testing suggest that similar to NICE guidelines that encourage gradual and controlled increases in activity to improve disease prognosis in CFS patients, that cognitive function may also be helped with gradual and controlled cognitive practise. ‘No funding sought for this study’

MG02
THE EFFECTS OF THE NOVEL MULTIMODAL ANTIDEPRESSANT VORTIOXETINE VERSUS THE SSRI PAROXETINE ON SLEEP ARCHITECTURE IN HEALTHY MEN: A PK/PD STUDY
Wilson SJ, Centre for Neuropsychopharmacology, Div of Brain Sciences, Imperial College London, Burlington Danes Bldg Hammersmith Campus, 160 Du Cane Rd London W12 0NN sue.wilson@imperial.ac.uk
Højer AM (2), Buchbjerg J (2), Areberg J (2), Nutt DJ (1) (1) Centre for Neuropsychopharmacology, Div of Brain Sciences, Imperial College London, 2. Lundbeck A/S, Clinical & Quantitative Pharmacology, Copenhagen-Valby, Denmark

Changes in sleep architecture are a sensitive measure of drug effects in the brain, and may be used to compare compounds with different pharmacologic profiles. Selective serotonin (5-HT) reuptake inhibitors (SSRIs) and drugs that act at 5-HT receptors (including 5-HT1A, 5-HT3, 5-HT7) give rise to acute detectable changes in sleep architecture, particularly in rapid eye movement (REM) sleep. Vortioxetine is a novel multimodal antidepressant for the treatment of major depressive disorder. It is a 5-HT3, 5-HT7 and 5-HT1D receptor antagonist, a 5-HT1A receptor agonist, a 5-HT1B receptor partial agonist, and an inhibitor of the serotonin transporter (SERT) [Mørk et al 2012 J Pharmacol Exp Ther 340, 666-675]. The purpose of this study was to compare the effect of vortioxetine, paroxetine and placebo on sleep architecture, as measured by polysomnography (PSG); it was expected that vortioxetine would affect REM sleep and that this effect would be different from that of an SSRI. This was a randomised, double-blind, four-way crossover, placebo-controlled, multiple-dose study in 24 healthy young men. Participants received 20 mg vortioxetine (n=20), 40 mg vortioxetine (n=24), 20 mg paroxetine (n=20), or placebo (n=20) for 3 consecutive days in 4 periods with at least 3 weeks between treatment periods. The dose of 40 mg vortioxetine for 3 days corresponds to the steady state plasma concentration with 20 mg. PSG recordings were performed on the pre-dose night, nights 1 and 3 of dosing in each period and were scored manually by an expert scorer blind to treatment, using standard methods. Blood samples were obtained for pharmacokinetic (PK) analysis. Plasma concentrations of vortioxetine and paroxetine during the PSG measurement were used to estimate SERT occupancies using published relationships between plasma concentration and SERT occupancy in healthy subjects [Areberg et al 2012 Basic Clin Pharmacol Toxicol 110, 401-404, Meyer et al 2004 Am J Psychiatry 161, 826-835]. In the pharmacodynamic (PD) analysis both drugs significantly increased REM onset latency (ROL) and decreased time in REM sleep (TREM) (p<0.0001). In the PK/PD analysis using an Emax model, there were significant relationships between both ROL and TREM and drug exposure for both vortioxetine and paroxetine. The relationship between REM suppression and SERT occupancy was significantly different between vortioxetine and paroxetine. For vortioxetine, REM onset latency started to increase at a higher SERT occupancy than after paroxetine. Vortioxetine effects on REM sleep showed a different relationship to estimated SERT occupancy from paroxetine, which is likely to reflect its additional actions at serotonin receptors. This study was sponsored by H. Lundbeck A/S as part of a joint clinical development programme with the Takeda Pharmaceutical Company, Ltd

MG03
THE CO-MORBIDITY OF MUSCULOSKELETAL DISORDERS AND SLEEP PROBLEMS IN ADOLESCENTS: ASSOCIATIONS WITH PAIN-RELATED AND SOMATIC FACTORS
Harrison L, Social and Community Medicine, Uni. of Bristol, BF1 Oakfield House, Clifton, Bristol, UK, BS8 2BN, lee.harrison@bristol.ac.uk
Wilson S (2) Munaro MR (3) (2) Dept of Medicine, Imperial College London, Hammersmith Campus W12 0NN; (3) Sch of Experimental Psychology, Uni of Bristol, 12a Priory Rd, Bristol BS8 1TU

Background: Around two thirds of adolescents with chronic pain report a concurrent sleep problem. The nature of these problems varies and can include extended sleep onset latencies, difficulty with sleep maintenance, and daytime hypersomnolence. Both chronic pain and sleep problems can
ALTERED CB1 RECEPTOR SIGNALLING IN THE LATERAL PAG OF WISTAR-KYOTO RATS IS ASSOCIATED WITH ENHANCED FORMALIN-EVOKED NOCICEPTIVE BEHAVIOUR COMPARED WITH SPRAGUE-DALWEY RATS

Jennings EM, Pharmacology and Therapeutics, National University Ireland Galway, University Rd, NUIG, Galway, Ireland, NA, e.jennings4@nuigalway.ie
Olango WM(1,3), Rea K(1,3), Okine BN(1,3), McGowan F(1,3), Roche M(2,3), Finn DP(1,3) (1) Pharmacology and Therapeutics; (2) Physiology, School of Medicine, National University of Ireland; Galway, Ireland. (3) NCBES Centre for Pain Research and Galway Neuroscience Centre, National University of Ireland, Galway, Ireland.

Wistar-Kyoto (WKY) rats display hyper-responsivity to stress and enhanced nociceptive responding compared with Sprague-Dawley (SD) rats (Burke et al. 2010. Neuroscience, 171: 1300-1313). The periaqueductal grey (PAG) is an important component of the descending inhibitory pain pathway and is also involved in stress coping. Recent evidence has shown that impaired functioning of the endocannabinoid system in the descending inhibitory pathway of WKY rats may contribute to their hyperalgesic phenotype (Rea et al., 2013. Pain, 155: 69-79). The aim of this study was to investigate whether altered expression and/or functionality of CB1 receptors in the PAG underlie hyperalgesia to formalin injection in WKY versus SD rats. Adult male SD and WKY rats (250-350g; n=6-12 per group) were used. Rats received intraplantar injection of saline or formalin and nociceptive behaviour was assessed, after which tissue levels of endocannabinoids and cannabinoid CB1 receptor mRNA in the PAG were measured by LC-MS-MS and qRT-PCR, respectively. A second cohort of SD and WKY rats received bilateral microinjection of vehicle or CB1 receptor agonist, arachidonyl-2-chloroethylamide (ACEA; 0.05pmol per side), into the lateral PAG (lPAG) and formalin-evoked nociceptive behaviour was assessed. Quantitative immunohistochemical analysis of c-Fos staining was carried out in the rostral ventromedial medulla (RVM) and superficial layers of the lumbar region of the spinal cord dorsal horn. Data were analysed by ANOVA and Fisher’s LSD (P<0.05 significant).

Drug-naive WKY rats exhibited greater formalin-evoked nociceptive behaviour than SD rats. In addition WKY rats had lower expression of CB1 receptor mRNA and increased levels of 2-arachidonoyl glycerol (2-AG) in the PAG, compared with SD rats. In SD rats, intra-PAG administration of ACEA produced a significant and prolonged reduction in formalin-evoked nociceptive behaviour. This intra-PAG ACEA-induced reduction in nociceptive behaviour in SD rats was associated with increased c-Fos expression in the RVM and decreased c-Fos expression in the spinal cord dorsal horn. In contrast, intra-PAG administration of ACEA to WKY rats potentiated nociceptive behaviour towards the end of the formalin trial. CB1 receptor activation in the IPAG of SD rats, but not WKY rats, reduces formalin-evoked nociceptive behaviour, with a concomitant increase in neuronal activity in the RVM and reduced neuronal activity in the dorsal horn of the spinal cord. In addition, enhanced formalin-evoked responding in WKY rats is associated with reduced expression of the CB1 receptor and increased tissue levels of the endocannabinoid, 2-AG, in the IPAG. Thus, alterations in the endocannabinoid system within the descending inhibitory pain pathway may contribute to the hyperalgesic phenotype of WKY rats.

Acknowledgements: Science Foundation Ireland (10/IN.1/B2976) and IRCSET
Anti-obesity drugs that cause weight loss by reducing energy intake have had limited success. Some patients exhibit substantial reductions in food intake, indicating that there might be differences in baseline fMRI BOLD signals in reward areas underlying disparate effects of the 5-HT2C receptor agonist meta-chlorophenylpiperazine on consumption of a palatable snack.

**COMPULSIVITY AND UNDERLYING FUNCTIONAL NEURAL NETWORKS IN HEALTH AND DISEASE**

**Morris LS**, Dept Psychiatry, Univ of Cambridge, Addenbrooke’s Hospital, Cambridge CB2 0QQ, lm601@cam.ac.uk

Kundu P (1), Irvine MA (2), Robbins TW (1,3), Bullmore ET (1,2), Voon V (1,2) 1. Behavioural and Clinical Neuroscience Inst, Univ of Cambridge, CB2 3EB 2. Dept of Psychiatry, Univ of Cambridge, Addenbrooke’s Hospital, Cambridge CB2 0QQ 3. Dept of Psychology, Downing Site, Univ of Cambridge, CB2 3EB

Compulsivity, the maladaptive persistence of inappropriate behaviours despite negative consequences, is a major hallmark of a range of psychiatric disorders, particularly addiction (Robbins et al, 2012, Trends in Cognitive Sciences, 16:1364-6613). A shift from flexible goal-directed to habitual compulsive behaviour is reflected in a shift from engagement of ventral striatal (VS) to dorsal striatal regions (Yin et al, 2004, European Journal of Neuroscience, 19: 181-189; Everitt and Robbins, 2005, Nature Neuroscience, 8: 1481-1489; O’Doherty et al, 2004, Science, 304: 452-454). We explored these relationships in a population of obese patients with and without binge eating disorder (BED) and healthy controls. We employed 3 measures of compulsivity and examined resting state functional connectivity in reversal learning (measuring behavioural adaptation following contingency shifts with outcome valence modulation); habit formation (measuring relative contribution of goal-directed or habitual control) and intra-extra-dimensional (IDED) shifting (measuring attentional set shifting). Compared to controls, patients with BED had a specific impairment in reversal learning in the context of reward whereas those with obesity were specifically impaired to loss. Similarly, BED were impaired in habit formation and extradimensional shifting. Reversal learning was associated with increased VS and dorsolateral PFC (dIPFC) connectivity across all groups. Reversal errors were associated with increased VS and orbitofrontal cortex (OFC) connectivity. Greater reliance on habit formation was associated with increased putamen and VS connectivity in healthy controls and VS and premotor across groups. Greater reliance on goal-directed behaviour reflected increased VS and mOFC connectivity. ED shift errors were associated with decreased connectivity between dIPFC and VS in all groups, but predominantly in BED patients. We provide evidence of impairments in behavioural flexibility in BED. We further map distinct but overlapping corticostriatal networks across compulsivity measures. This research was supported by a grant from the Wellcome Trust.

**INCORPORATED NEURAL RESPONSES TO ANTICIPATION AND CONSUMPTION OF REWARDING AND AVERSIVE STIMULI IN SISTERS OF THOSE WITH ANOREXIA NERVOSA**

**Horndasch S**, School of Psychology and Clinical Language Sciences, Univ of Reading, Whiteknights Rd, Reading UK, RG6 6AL, s.horndasch@reading.ac.uk

Rzepa E, McCabe C School of Psychology and Clinical Language Sciences, Univ of Reading, Whiteknights Rd, Reading RG6 6AL

Introduction: Abnormal brain reward responses and increased cue reactivity towards food stimuli have been shown in those suffering from eating disorders (Frank et al., 2012, Neuropsychopharmacology, 37, 2031-2046; Zhu et al., 2012, European Eating Disorders Review, 20, 439-50). We have shown that those “at risk” by virtue of having had anorexia nervosa in the past have increased neural responses to rewarding and aversive food stimuli (pictures and taste of chocolate and aversive pictures and taste) compared to healthy control participants (Cowdrey et al., 2011, Biological Psychiatry, 70, 736-743). However it is not yet known if these differences are true trait markers or simply scars from having had the illness. Thus our aim was to examine another “at risk” group but before illness onset, i.e. sisters of anorexia nervosa patients. Methods: We used a between subject design whereby healthy females (18 to 45 years old) who have a sister with current or a history of anorexia nervosa and gender matched control participants performed a reward task based on (McCabe et al., 2009, Psychopharmacology, 205, 667-677). Using fMRI we measured the neural response to the anticipation (picture of chocolate drink) and receipt of reward (chocolate taste) and aversive picture (picture of moldy drink) and aversive taste (chocolate and beetroot). Results: Using SPM8 analyses we found a significantly increased activation in the sisters of anorexia nervosa patients compared to the healthy controls in the rewarding chocolate picture condition in the hippocampus (p=0.02, small volume corrected) and in the rewarding chocolate taste condition in the hippocampus and insula (p=0.05 and p=0.04, small volume corrected). We also observed significantly increased activation to the aversive picture condition in the occipital cortex and posterior cingulate (p=0.05 and p=0.04, small volume corrected) and to the aversive taste condition in the dorsal cingulate cortex (p=0.02, small volume corrected) in the sisters of anorexia nervosa patients compared to the control participants. Conclusions: Our preliminary findings suggest greater activation in key regions of the brain that are known to process rewarding and aversive taste stimuli. The results are consistent with previous data showing increased responses to food reward and aversive stimuli in recovered anorexia nervosa patients. These findings for those “at risk” for an eating disorder but without the confounds of anorexia nervosa personal history support the idea that neural responses to food stimuli might be a trait marker for anorexia nervosa. This research is funded by a start-up fund from the University of Reading for Dr McCabe.

**DIFFERENCES IN BASELINE FMRI BOLD SIGNALS IN REWARD AREAS UNDERLY DISPARATE EFFECTS OF THE 5-HT2C RECEPTOR AGONIST META-CHLOROPHENYLPIPERAZINE ON CONSUMPTION OF A PALATABLE SNACK**

**Thomas JM**, School of Psychology, Univ of Birmingham, Frankland Bldg, Edgbaston Birmingham, B15 2TT, thomasjm@bham.ac.uk

Dourish CT(2), Tomlinson JW(3), Hassan-Smith Z(3), Hansen P(1), Higgs S(1) (1) School of Psychology, Univ of Birmingham, Edgbaston B15 2TT; (2) P1vital, Manor House, Howbery Park, Wallingford, Oxfordshire, OX10 8BA; (3) Centre for Endocrinology, Diabetes and Metabolism, School of Clinical and Experimental Medicine, Univ of Birmingham, Birmingham, B15 2TH

Anti-obesity drugs that cause weight loss by reducing energy intake have had limited success. Some patients exhibit substantial reductions in food intake, indicating that there might be differences in baseline fMRI BOLD signals in reward areas underlying disparate effects of the 5-HT2C receptor agonist meta-chlorophenylpiperazine on consumption of a palatable snack.

**ABSTRACTS**
intake, whereas others show little to no response. It is conceivable that differences in brain responses to food stimuli between drug responders and non-responders could help identify factors which determine these disparate responses. In the present study, 24 healthy female participants were dosed with placebo or 30mg mCPP on separate test days a week apart in a double-blind cross-over design. On test days, participants were scanned twice using fMRI at baseline, and after dosing, and viewed images of high calorie foods. Participants were then satiated with a lunch of pasta, and subsequently given ad-libitum access to a high calorie cookie snack. Twenty participants completed testing, and were classified either as responders if they showed a > 10% decrease in cookie consumption after mCPP vs. placebo (12 participants) or non-responders if they showed a < 10% decrease in cookie consumption after mCPP (8 participants). mCPP decreased cookie consumption by responders (-24%), and increased consumption by non-responders (+6%) (p < 0.001). Analysis of ratings of cookie pleasantness showed that non-responders rated the cookies as significantly more pleasant, than responders (p < 0.05), in the absence of any differences in hunger (p = 0.96). After subtracting placebo scans, a whole-brain cluster-corrected analysis showed an interaction between group (responders vs. non-responders) and time (pre vs. post mCPP). Analysis of local maxima revealed that at baseline, non-responders exhibited greater BOLD activity than responders in key reward/motivational centres (midbrain, pons, amygdala, parahippocampal gyrus, putamen, posterior cingulate cortex, insula, orbitofrontal cortex and dorsomedial prefrontal cortex (all p < 0.001), to the sight of high calorie food images. The results suggest that non-responders to mCPP show a greater reward response to high calorie foods at baseline, which may be responsible for their enhanced ratings of cookie pleasantness. Together, these results evoke the novel concept that administration of an appetite suppressant to individuals who exhibit enhanced reward responses to food stimuli may be associated with a reduction in the satiating effect of the drug and in some participants increased food intake. Jason Thomas is supported by the Steve Cooper Ph.D. CASE studentship funded by the BBSRC and P1vital.

MH04

ENHANCED NEURAL RESPONSE TO REWARD AND AVERSION FOLLOWING SINGLE TREATMENT WITH THE CANNABINOID CB1 NEUTRAL ANTAGONIST THCV IN HEALTHY VOLUNTEERS

McCabe C, Psychology, Univ of Reading, Whiteknights Campus, Reading, RG66AL, c.mccabe@reading.ac.uk
Tudge L(1), Williams C(2), Cowen P(2), (1) Dept Psychology, Univ of Reading (2) Dept Psychiatry, Univ of Oxford

Background: Disturbances in the regulation of reward and aversion in the human brain may underlie many psychiatric disorders from obesity to clinical eating disorders and addictions. Using a model to assess reward and aversion we have shown that the cannabis receptor (CB1) inverse agonist, rimonabant (an anti-obesity drug removed from the market due to depression side effects) diminished neural responses to reward yet increased responses to aversive stimuli (Horder et al, 2010; Int J Neuropsychopharmacol.13(8):1103-13). Interestingly this pattern is similar to that seen in patients at high risk of depression in our model (McCabe et al, 2009; Psychopharmacology (Berl).205:667-677) and suggests a mechanism by which depression might be induced by rimonabant. THCV is a component of Cannabis sativa, and unlike rimonabant acts as a neutral CB1 receptor antagonist (Pertwee, 2008; Br J Pharmacol. 153:199-215) and could therefore be free of depressogenic side effects (Le Foll et al, 2009; Psychopharmacology (Berl).205:171-174). We therefore hypothesized that THCV would, unlike rimonabant, leave intact the neural response to reward but augment the response to aversive stimuli. Methods: We used a within-subject, double-blind design, where 20 healthy volunteers were treated with a single dose of THCV (10mg) and placebo in a randomised order. We used fMRI to measure the neural response to rewarding (sight and/or flavour of chocolate) and aversive stimuli (sight of mouldy strawberries and/or an unpleasant strawberry taste). Volunteers also rated the pleasantness, intensity and wanting for each of the stimuli. fMRI testing took place on two occasions (a) about one hour after administration of THCV (b) about one hour after administration of placebo. Results: There were no significant differences between the groups in subjective ratings; however, THCV augmented activation to the chocolate stimuli, in key reward areas such as the anterior cingulate cortex, the thalamus (p<0.001 whole brain corrected) and the putamen (p=0.03 small volume corrected). THCV also increased neural responses to the aversive stimuli condition in the amygdala, insula, caudate and hippocampus (p=0.03, p=0.005, p=0.005 whole brain corrected) and in the anterior cingulate, thalamus, medial frontal gyrus and the putamen (all p<0.001 whole brain corrected). Conclusions: Our findings are the first to show that treatment with the CB1 neutral antagonist THCV potentiates neural responding to rewarding and aversive stimuli in contrast to rimonabant, an inverse agonist. The profile of effect of THCV could suggest therapeutic activity in certain eating and metabolic disorders, perhaps with a lowered risk of depressive side effects. Funded by GWpharma.

MH05

EFFECT OF SHORT-TERM FASTING ON IMPULSIVE AND COMPULSIVE BEHAVIOUR: A TWO-PART STUDY IN A NON-CLINICAL POPULATION

Howard M, Clinical Educational Health Psychology, University College London, 1-19 Torrington Place, London, WC1E 7HB, maxine.howard.11@ucl.ac.uk
Roiser J(2), Gilbert S(2), Burgess P(2), Dayan P(3), Serpell L(1) 1Dept of Clinical, Educational and Health Psychology, UCL, 2 Inst Cognitive Neuroscience, UCL 3Gatsby Computational Neuroscience Unit, UCL

Bulimia Nervosa (BN) has been characterised as a disorder of poor impulse control. However, there have been mixed findings from studies comparing impulsivity in individuals with BN and Healthy Controls (HCs). These mixed findings could be partially due to differences in metabolic state. Individuals with BN undergo periods of short-term fasting and may not be comparable to satiated HCs. Research has shown that short-term fasting in HCs is associated with changes in risky decision making. Therefore Experiment 1 was designed to examine the influence of short-term fasting on four types of impulsivity: risky decision-making, action inhibition, impulsive choice, and reflection impulsivity. HCs were tested twice, once when fasted for 20 hours, and once when satiated. Participants made significantly more errors of action inhibition, during an Affective Shifting Task and opened more boxes in the Fixed Win (FW) condition of the Information Sampling Task (IST) when fasted, indicating decreased reflection
impulsivity. There were no significant differences for risky decision-making or impulsive choice. Experiment 2 used a similar design. The IST, a measure of central coherence, and a set-shifting task were used in order to determine whether the increased box opening when fasted, was explained by decreased reflection impulsivity, set-shifting difficulties, or weaker central coherence. Experiment 2 did not replicate findings from Experiment 1; there was no significant difference in IST responses between fasted and satiated sessions. Furthermore, fasting did not influence measures of set-shifting or central coherence. The results from Experiment 2 indicate that the influence of fasting on cognitive functioning is variable. However the influence of short-term fasting on measures of impulsivity in Experiment 1 suggest that differences in metabolic state need to be considered when investigating differences in impulsivity between BN and HC.

*This research was funded by a studentship award from the Medical Research Council.

MH06

TRAINING RESPONSE INHIBITION TO FOOD TO REDUCE OVEREATING

Lawrence NS, Psychology, Univ of Exeter, Univ of Exeter, Perry Rd, Exeter EX4 4QG, Natalia.Lawrence@exeter.ac.uk
Verbruggen F(1), Morrison S (2), Parslow DM (1), O’Sullivan J (1), Javaid M (1), Adams RC (2), Chambers CD (2) (1) Dept of Psychology, Univ of Exeter, Perry Rd, Exeter EX4 4QG (2) School of Psychology, Cardiff Univ, Park Place, Cardiff CF10 3AT

Most UK adults (62%) are overweight or obese, costing the NHS over £5 billion a year. Computerised response inhibition training could improve self-control in individuals who overeat. Training people to inhibit simple motor responses (key presses) to specific food pictures reduces the subsequent consumption of those foods by up to 40%. We examined whether different types of response inhibition training modify eating behaviour in the lab and at home. Our first between-subjects lab experiment (N = 65) compared the effects of stop vs. dual (two key-presses) response training to food pictures on immediate consumption of one snack food (crisps). Our second study (N = 170) offered two foods (crisps and chocolate), one of which was not associated with stopping, to enable within- and between-subjects comparisons of intake. We also added a control condition in which participants had to ignore stop signals and respond with one key-press to all pictures. Our third lab experiment (N = 170) compared the effects of stop vs. dual response training to non-food pictures. Finally, we conducted a pilot randomised controlled trial in a community sample (N = 87) to examine whether repeated no-go training to food vs. non-food pictures, delivered via the internet, modified real world eating behaviour. Daily snacking, 24-hour food diaries, food stimulus ratings and weight were measured before and after one week (4 sessions) of no-go training. Our first study showed significant (p < .05) reductions in crisp intake following food-related stop vs. dual response training. Our second study showed no overall effects of training (food-related stop, dual or ‘ignore’ control), but effects were moderated by dietary restraint. Restrained eaters ate less following stop vs. dual, but not vs. control training. Our third experiment showed no effect of general (non-food) stop vs. dual response training. Our pilot RCT suggested significant reductions in weight, food ratings and calorie intake (food diaries), but not self-reported snacking frequency, following repeated food no-go training. These findings suggest some stimulus-specific effects of response inhibition training on food intake that are moderated by dietary restraint. However, lab studies may be confounded by increased food intake in the dual-response comparison groups, consistent with the effects of food cue exposure increasing intake. Nevertheless, our pilot RCT indicates promising effects of food-associated response inhibition training on weight loss. Excellent adherence (94%) to, and positive feedback about the training further suggests it has the potential to reduce overweight and obesity. This work was generously supported by a Wellcome Trust Institutional Strategic Support Award (WT097835MF).

MH07

SURPRISING LACK OF INTERACTION BETWEEN INDIVIDUALLY SUB-MAXIMAL ANORECTIC DOSES OF EXENDIN-4 AND NALTREXONE

Rodgers RJ, Inst Psychol Sci, Univ Leeds, Woodhouse Lane, Leeds UK, LS2 9JT, r.j.rogers@leeds.ac.uk
Wright FL Inst Psychol Sci Univ Leeds Woodhouse Lane Leeds LS2 9JT

The relative lack of success of drug monotherapies for appetite control and weight loss has recently prompted considerable academic and commercial interest in the potential advantages of drug polytherapy (Rodgers et al, 2012, Disease Models and Mechanisms, 5: 621-626). In this context, it has been established for many years that broad-spectrum opiate receptor antagonists, such as naloxone and naltrexone, not only suppress food intake in a behaviourally-selective manner but interact additively with other anorectic agents (e.g. cannabinoid CB1 receptor antagonists, Tallett et al, 2008, Physiology & Behavior, 94: 422-431; and bupropion, Wright & Rodgers 2013, Psychopharmacology, 228: 291-307). Exendin-4, an enzyme-resistant, high affinity agonist for GLP-1 receptors, shares many of the effects of GLP-1 including stimulation of insulin secretion, reduction in glucose levels, delayed gastric emptying, and inhibition of food intake (Barrera et al., 2011, Nature Reviews Endocrinology, 7: 507-516). We have recently shown that, when administered systemically, exendin-4 dose-dependently inhibits the intake of palatable food and the frequency of feeding behaviour in rats (Wright & Rodgers, 2013 Behavioural Pharmacology, 24 (Online Supplement): pp e1-e64, G.11). However, at higher dose levels (2.5 µg/kg IP), these effects were accompanied by a suppression of all active behaviours and a disruption of the behavioural satiety sequence (BSS). In the present study, we have assessed the effects of combined treatment with sub-maximal anorectic doses of exendin-4 (0.025 or 0.25 µg/ kg) and naltrexone (0.1 mg/kg) on food intake and behaviours (ingestive & non-ingestive) in thoroughly habituated, non-deprived male rats during 1h tests with palatable mash. A within-subjects design was employed, with treatment order determined by Latin Square and a washout period of 7-days. Exendin-4 (or vehicle) was administered 15 min prior to naltrexone (or vehicle), with animals placed into the test arena 15 min following the second injection. Test sessions were DVD-recorded and scored blind to treatment condition. Datasets were subjected to repeated measures ANOVA and Bonferroni comparisons. The results confirmed that exendin-4 (0.25 µg/kg) and naltrexone each produced a significant reduction (35-40%) in mash consumption (p < 0.001 vs vehicle control) while inhibiting feeding behaviour and accelerating an otherwise normal BSS. Most surprisingly, however, these treatments in combination (35% reduction vs vehicle) failed to exert stronger anorectic effects than those obtained with either agent given alone. This outcome suggests that the exendin-4/naltrexone combination results in some form of pharmacokinetic and/or pharmacodynamic interference that would appear to strongly undermine therapeutic potential. This study received no financial sponsorship.
TA01

UNIVERSITY STUDENTS USE, AWARENESS AND PREVALENCE OF PRESCRIPTION STIMULANTS IN A UK STUDENT POPULATION AND THE INFLUENCE OF PERSONALITY

Pennington K, Psychology, Univ of Lincoln, Brayford Pool Bridge House, Rm 1102 Lincoln LN6 7TS, kpennington@lincoln.ac.uk
Moore A. Univ of Lincoln

Cognitive enhancement though the use of prescription stimulants is thought to be on the rise particularly in certain settings such as university campuses (Ragan et al., 2013, Neuropharmacology, 64, 588-595). However, much of the empirical evidence for this comes from American student populations. This study presents the findings from a pilot study which aimed to investigate the awareness and beliefs concerning cognitive enhancement in a cross-sectional UK student population. The study reported consisted of 113 students from multiple UK university institutions (mean age 20.72 (SD 2.01); 38M, 75F) studying subjects across arts, science and the social sciences. An online questionnaire, designed using Qualtrics was distributed via social media sites. It was found that 72 (63.7%) of the population were aware of either Ritalin, Adderall or Modafinil. Of these, 19 (37.9%) had friends who had taken these substances but only 3 (4.2%) had taken them themselves. Those that were most aware of prescription stimulants had significant differences in what they thought these substances were used for in comparison with those who were unaware (χ² (2, N=113, p<0.001). There was no significant difference in awareness of the substances due to gender, university type (pre- or post- '92) or course type. In the whole population, 46% thought that substances which may enhance cognition should be allowed for all students with restrictions. In terms of personality effects, ANOVA analysis found that there were significantly higher extraversion scores in the group that thought cognitive enhancers should be allowed without restrictions (p<0.05). None of the other ‘Big 5’ measures were significantly different between the responses to beliefs about enhancing cognition. This preliminary study indicates that awareness of prescription stimulants is fairly high but use is relatively low in comparison with some other published studies (i.e. Varsity, 2009 Varsity, 693, 1-5; Holloway & Bennett 2012 Drugs: Education, Prevention & Policy, 19, 137-144). However, students were found to agree with the use in principle and with restrictions suggesting that if these substances became more readily accessible on University campuses students would not be averse to using them. Future work should further establish the prevalence and awareness of prescription stimulants is in a what ‘restrictions’ students think should be in place for the endorsement of the use of these prescription stimulants to be acceptable and what might influence them to take these substances themselves. This would further investigate the prevalence of prescription stimulant use for cognitive enhancement by student populations and the effect this might have on others.

TA02

METHYLPHENIDATE EFFECTS ON BRAIN ACTIVITY AS A FUNCTION OF SLC6A3 GENOTYPE AND STRIATAL DOPAMINE TRANSPORTER AVAILABILITY

Ettinger U, Dept of Psychology, Univ of Bonn, Kaiser-Karl-Ring 9 Bonn, Germany, 53111, ulrich.ettinger@uni-bonn.de
Kasparbauer AM(1), Rujescu D(2), Riedel M(3,4), Pogarell O(3), Costa A(3), Meindl T(5), la Fougère C(6,7) (1) Dept of Psychology, Univ of Bonn, Bonn, Germany (2) Dept of Psychiatry, Univ of Halle, Halle, Germany (3) Dept of Psychiatry, Univ of Munich, Munich, Germany (4) Clinic for Psychiatry, Psychotherapy, Gerontopsychiatry and Neurology, Rottweil, Germany (5) Inst of Clinical Radiology, Univ of Munich, Munich, Germany (6) Dept of Nuclear Medicine, Univ of Munich, Munich, Germany (7) Dept of Nuclear Medicine, Univ of Tubingen, Tubingen, Germany

We pharmacologically challenged catecholamine reuptake in order to investigate its effects on brain activity during a response inhibition task as a function of the 3´-UTR variable number of tandem repeats (VNTR) polymorphism of the dopamine transporter (DAT) gene (SLC6A3) and the availability of DATs in striatum. This VNTR has previously been found to be related to clinical response in patients with ADHD in naturalistic study designs (Kambetz et al 2014 Pharmacogenomics Journal 14:77-84). Here, we measured the hemodynamic response of 50 healthy males (age mean=23.72 years, SD=3.05, range 18-31) during a Go/No-Go task, a measure of cognitive control, under the influence of 40mg methylphenidate and placebo using 3T functional magnetic resonance imaging (fMRI). Subjects were grouped into 9-repeat (9R) carriers and 10/10 homozygotes on the basis of the SLC6A3 VNTR. This grouping was carried out due to the small number of 9R homozygotes (here N=5), in line with previous work (e.g. Costa et al 2011 Synapse 65:998-1005). During successful inhibition of a motor response, methylphenidate induced an increase of blood-oxygen-level-dependent (BOLD) signal for carriers of the SLC6A3 9R-allele but a decrease in 10/10 homozygotes in brain areas associated with motor inhibition. We additionally investigated in a subset of 35 participants whether baseline striatal DAT availability, ascertained with 123I-FP-CIT single photon emission computed tomography (SPECT), predicted the amount of methylphenidate-induced change in hemodynamic response or behavior. Striatal DAT availability was nominally greater in 9R carriers compared to 10/10 homozygotes (d=.40), in line with meta-analyses, however did not predict BOLD or behavioral changes following MPH administration. We conclude the effect of acute MPH administration on brain activation is dependent on DAT genotype, with 9R carriers showing enhanced BOLD following administration of a pro-dopaminergic compound.

Funding: The study was supported by the DFG Emmy Noether Programme (ET 31/2-1). SPECT scans were additionally supported by a grant from GE Healthcare.
MONOAMINE EFFECTS ON SOCIAL LEARNING

Campbell-Meiklejohn DK, The Inst for Clinical Medicine (Aarhus), Dept of Psychology (Cambridge), Aarhus Univ & Univ of Cambridge, Dept of Psychology, Downing St Cambridge, CB2 3EB, dc570@cam.ac.uk
Simonsen, A (1), Scheel-Kruger J J (1), Jensen M (1), Møller A (1), Roepstorff A (1) & Frith CD (1) (1) Center for Functionally Integrative Neuroscience, Norrebrogade 44, Bldg 10G, 5th Floor, Aarhus, 8000, Denmark

Introduction: The ability to infer subjective value by observing choices of other people is an essential ability with a poorly understood neurobiology. In two studies we identified distinct effects of a serotonin manipulation (citalopram) and catecholamine manipulation (methylphenidate (MPH, ritalin) on a task measuring social conformity. Methods: In all, 58 healthy adult females received either a single oral 20 mg dose of MPH, 40mg of citalopram, or a placebo (PL). Each subject rated 153 faces on a scale of apparent trustworthiness followed immediately by the face’s mean rating from a group of anonymous peers. After 30 min and a 2-back continuous-performance working-memory task, subjects were unexpectedly asked to rate all the faces again. Results: All groups tended to change their own ratings toward the social norms. The MPH group exhibited twice the conformity effect of the PL group following moderate social conflicts with the norms, but MPH had no effect on large conflicts of opinion. MPH did not affect 2-back performance. Conclusions: Catecholamines appear to mediate behaviourally responses to subtle social conflicts, providing a theoretical route to increased conformity following treatment with ritalin for Attention Deficit Hyperactivity Disorder. In contrast, serotonin systems may mediate the impact of negatively valenced information on beliefs and behaviour, be it information gained by direct observation or information gained from the opinions of third parties. Together the effects indicate distinct influences of different monoamines when learning from the choices of others. Funded by Danish Council For Strategic Research and Danish Council for Independent Research grants to DCM.

THE INFLUENCE OF COMT GENOTYPE AND AFFECTIVE DISTRACTORS ON SELF-GENERATED THOUGHT

Kilford EJ, Inst of Cognitive Neuroscience, Univ College London, 17 Queen Square, London, WC1N 3AR, e.kilford.12@ucl.ac.uk
Dumontheil I (1,2), Blakemore S-J (1) (1) Inst of Cognitive Neuroscience, Univ College London, 17 Queen Square, London WC1N 3AR (2) Dept of Psychological Sciences, Birkbeck, Univ of London, Malet St, London WC1E 7HX

Introduction: The catechol-O-methyltransferase enzyme (COMT) is a major determinant of prefrontal dopamine levels (Witte & Flöel, 2012, Brain Res Bull, 88, 418-428). A common functional polymorphism, Val158Met, affects COMT enzymatic activity and has previously been associated with variation in executive function and affective processing (Mier et al., 2010, Mol Psychiatr, 15, 918-927). Rationale: We investigated the association between Val158Met genotype and (1) the flexible modulation of the balance between the processing of self-generated, stimulus-independent information as opposed to perceptually based stimulus-oriented, information and (2) the impact of affective distractors. Methods: A group of 124 healthy adults, genotyped for the Val158Met polymorphism, performed a behavioural task in which alternating blocks of self-generated and stimulus-oriented information were processed. The task was additionally modified to allow examination of the influence of affective distractors on performance. Results: Relative to Val carriers, individuals homozygous for the Met allele made fewer errors when selecting and manipulating self-generated thoughts (p = .008). We also found a complex interaction between the influence of affective distractors, genotype and sex on task accuracy (p < .018): male, but not female, participants showed sensitivity to the affective distractors that was dependent on COMT genotype. Conclusions: This study provides evidence of the role of dopaminergic genetic variation on a novel aspect of executive function: the ability to select and manipulate self-generated information. The results also suggest sexurally dimorphic effects of Val158Met genotype on the influence of affective distractors on executive function. This research was funded by the Leverhulme Trust.

THE EFFECTS OF PSILOCYBIN AND MDMA ON BETWEEN-NETWORK RESTING STATE FUNCTIONAL CONNECTIVITY IN HEALTHY VOLUNTEERS

Roseman LR, Medicine, Imperial College London, Hammersmith Campus, Du Cane Rd London W12 0NN, leor.roseman13@imperial.ac.uk
Leech R (1), Fielding A (2), Nutt DJ (1), Carhart-Harris RL (1) (1) Dept of Medicine, Imperial College London, Hammersmith Campus, Du Cane Rd, London W12 0NN; (2) The Beckley Foundation, Beckley Park, Oxford OX3 9SY

Perturbing a system and observing the consequences is a classic scientific strategy for understanding a phenomenon. Psychedelic drugs perturb consciousness in a marked and novel way and thus are powerful tools for studying its mechanisms. In the present analysis, we measured changes in resting-state functional connectivity (RSFC) between a standard template of different independent components analysis (ICA)-derived resting state networks (RSNs) under the influence of two different psychoactive drugs, the stimulant/psychedelic hybrid, MDMA, and the classic psychedelic, psilocybin. Both were given in placebo-controlled designs and produced marked subjective effects, although reports of more profound changes in consciousness were given after psilocybin. For many RSN pairs, between-network RSFC was generally increased under psilocybin (p < .05, FDR corrected), implying that networks become less differentiated from each other in the psychedelic state. Decreased RSFC between visual and sensorimotor RSNs was also observed. MDMA had a notably less marked effect on between-network RSFC. The extensive changes observed under psilocybin may be exclusive to classic psychedelic drugs and related to their especially profound effects on consciousness. The novel analytical approach applied here may be applied to other altered states of consciousness to improve our characterization of different conscious states and ultimately advance our understanding of the brain mechanisms underlying them. Financial Sponsorship: The Beckley Foundation.
EVIDENCE THAT TRAIT IMPULSIVITY IS ASSOCIATED WITH HUMAN LIMBIC GABA-A RECEPTOR AVAILABILITY

Stokes PRA, Centre for Neuropsychopharmacology, Div of Brain Sciences, Imperial College London, 5th Floor, Burlington Danes Bldg, Hammersmith Hospital Campus, 160 Du Cane Rd, London, UK, W12 0NN paul.r.stokes@kcl.ac.uk

Myers JF(1,3), Benecke A(2), Kalk NJ(1), Watson BJ(3), Erritzoe D(1), Riaño Barros DA(4), Hammers A(4,5), Turkheimer FE(6), Nutt DJ(1), Lingford-Hughes AR(1) (1) Centre for Neuropsychopharmacology, Div of Brain Sciences, Burlington Danes Bldg, Imperial College London, W12 0NN, UK (2) Univ of Amsterdam, Amsterdam, Netherlands (3) Psychopharmacology Unit, School of Social and Community Medicine, Univ of Bristol, Oakfield House, BS8 2BN, UK (4) MRC Clinical Sciences Centre and Division of Medicine, Imperial College London, Hammersmith Hospital, UK (5) The Neurodis Foundation, CERMEP Imagerie du Vivant, Lyon, France (6) Centre for Neuroimaging Sciences, Inst of Psychiatry, PO89, De Crespigny Park, London SE5 8AF, UK

Introduction: Impulsivity is a personality trait which encompasses the tendency to initiate actions without forethought and the inability to inhibit inappropriate behaviour. Impulsivity plays an important role in a number of psychiatric disorders including addictions, ADHD and impulse control disorders. Despite promising preclinical evidence that impulsivity may be mediated by variation in the inhibitory ɣ-aminobutyric acid (GABA) neurotransmitter system, few studies have investigated this in humans. The aim of this study was to use [11C]Ro15 4513 positron emission tomography (PET) imaging to examine whether impulsivity is associated with variation in human GABA-A receptor availability. [11C]Ro15 4513 is an inverse agonist PET tracer which binds to the GABA-A receptor benzodiazepine site and may be sensitive to changes in synaptic GABA levels. Methods: 12 healthy male participants (mean age 48±6.8 years) with no history of cigarette smoking were imaged using [11C]Ro15 4513 PET. Only participants without a history of cigarette smoking were included in the study as previously we found that [11C]Ro15 4513 PET binding was higher in participants with a history of cigarette smoking (Stokes et al 2013 NeuroImage 69 70-77). Spectral analysis was used to quantify GABA-A receptor availability in the following regions of interest (ROIs): nucleus accumbens, caudate, putamen, substantia nigra and globus pallidus. These regions are thought to be critical for the regulation of impulsivity by GABA (Hayes et al 2014 European Journal of Neuroscience 1-12). Impulsivity was assessed in each participant using the Eysenck Impulsivity, Venturesomeness and Empathy questionnaire (EPQ-IVE). Results: GABA-A receptor availability significantly correlated with EPQ-IVE impulsivity scores in the right nucleus accumbens (r=0.60, p=0.04), left putamen (r=0.57, p=0.05) and the bilateral substantia nigra (r=0.57, p=0.05). No significant correlations were found between EPQ-IVE scores and GABA-A receptor availability in the caudate or globus pallidus. Conclusions: The results of this study indicate that limbic GABA-A receptor availability is associated with human impulsivity as measured by the EPQ-IVE. They suggest that variation in limbic GABA-A receptor availability may be an important determinant of human trait impulsivity. These findings have important implications for better understanding the neurobiology of disorders where impulsivity is abnormal, such as addiction and ADHD. This study was supported by the Medical Research Council, UK.

THE EFFECT OF ACUTE STRESS AND CORTISOL ON ENCODING AND RETRIEVAL: A SYSTEMATIC REVIEW OF THE LITERATURE WITH META-ANALYSIS

Symonds CS, Neuroscience & Psychiatry Unit, Inst of Brain, Behaviour & Mental Health, Univ of Manchester, 3.304 Jean MacFarlane Bldg., Oxford Rd, Manchester, M13 9PL, catherine.symonds@manchester.ac.uk

Henson CC (2), Deakin JFW (1), Anderson IM (1) (1) NPU, G.700 Stopford Bldg, Univ of Manchester, Oxford Rd, Manchester M13 9PL (2) Translational Medicine, Dept of Gastroenterology, Salford Royal Hosp, Salford M6 8HD

Background: An acute rise in corticosteroid has been shown to affect memory; however the evidence to date is unclear, with studies reporting both improved and impaired declarative memory (1). The timing of the rise in cortisol (prior to encoding or prior to retrieval); emotional aspects of the neurocognitive task and the method by which the cortisol rise was induced (exogenous drug administration or endogenous, stress-induced) also appear to affect participants ability to recall words. This systematic review with meta-analysis aimed to examine the acute effects of corticosteroids on declarative memory in 25 studies. Methods Medical databases and citation lists of included studies and relevant reviews were searched to identify trials using a priori selection criteria, namely randomised controlled trials of healthy volunteers with an acute cortisol rise induced by exogenous drug administration or stress task as well as encoding or retrieval were assessed on quantified tests of word learning. Meta-analysis was performed using the generic inverse variance method displayed with heterogeneity to allow pooling of studies which measured outcomes on different scales. The effect of neutral, positive and negative stimuli material was also examined in subgroup analyses. Results: Raised cortisol prior to retrieval, but not encoding, adversely affected performance in memory tasks. The effect was most consistently seen with exogenous cortisol and with the retrieval of neutral words. However, there were too few studies to draw firm conclusions regarding the effect of exogenous versus endogenous cortisol and the role of emotional material. Conclusions: The timing of the acute rise in cortisol related to encoding is important with a significant result only being found when there was a rise of cortisol post-encoding and pre-retrieval. This is most likely to represent a non-genomic action of cortisol given the rapid onset of the effect. The impact of emotional content of memories in the context of acute stress needs to be studied further. (1) Sauro, M.D. etal. (2003). Stress 6(4): 235-245. Funding: This work was supported by a clinical fellowship from NIHR Manchester Biomedical Research Centre.
TA08
MULTIVARIATE PATTERN RECOGNITION OF FMRI REVEALS DIFFERENT EFFECTS OF SCOPOLAMINE ACROSS LEARNING

Kotoula V, Dept of Neuroimaging, Centre for Neuroimaging Sciences, Inst of Psychiatry, Kings College London, DeCrespigny Park, Denmark Hill, London, SE5 8AF, vasileia.kotoula@kcl.ac.uk
Joules R(1) Mehta MA(1) (1) Dept of Neuroimaging, Centre for Neuroimaging Sciences, Inst of Psychiatry, Kings College London, De Crespigny Park, Denmark Hill, London, SE5 8AF

Introduction: Cholinergic projections in the brain innervate a wide network of brain regions and play a fundamental role in cognitive processes. Scopolamine, a non-selective muscarinic receptor antagonist, has been widely used to study the role of the cholinergic system in cognition. In the present study, an FMRI Paired Associates Learning (PAL) task was used to assess the effect of scopolamine on the pattern of brain regions activated during the encoding of visual spatial associations. We hypothesized scopolamine would reduce brain activity in a distributed pattern of brain areas including the hippocampus. Methods: In this double-blind, placebo controlled, cross–over BOLD fMRI (TR=2000ms, TE= 40ms) study, scopolamine (s.c 0.2mg) or placebo were administered to 16 healthy volunteers who were scanned while performing the PAL task. During the task, three repeated phases of active encoding and retrieval of visual-spatial associations are followed by a control condition, where no active encoding or retrieval is required. To investigate the temporal dynamics of the experimental conditions, Gaussian Process Classification (GPC) was applied to data from a 2 volume, moving, average, box-car window. Weight maps and t-maps were generated for each comparison and the pattern of brain regions highly weighted for each task phase as well as for scopolamine were examined. Results: Significant classification accuracies (>70%) were obtained for active encoding compared to the control condition, in the placebo group. Furthermore, scopolamine was discriminated from placebo during all encoding phases (Phase I 81.25%, Phase II 81.25%, Phase III 75%; p<0.01 corrected for multiple comparisons). Some significant classifications were also obtained for retrieval. The pattern of discrimination for active encoding, compared to control encoding, included the anterior cingulate cortex, superior parietal regions, the visual cortex, as well as the hippocampus. A distributed pattern of brain regions, including the middle and posterior cingulate cortex, the insula, the parahippocampal gyrus and the hippocampus presented with increased activations for scopolamine compared to placebo. Discussion: The novel methodology developed for this study allowed identification of the brain patterns which were consistently activated during the task and were affected by scopolamine. In addition to the identification of a clear learning network, widespread effects of scopolamine were also demonstrated. Notably, the effects of scopolamine, on encoding depended on the stage of learning. Moreover, brain areas such as the hippocampus, which had previously been identified as scopolamine targets, presented with increased activation and might suggest the existence of compensatory mechanisms. Acknowledgements: Data collection was supported by a research grant from GSK. Data analysis was supported by the Innovative Medicines Initiative: NEWMEDS

TA09
THE GENERALISATION OF EMOTION RECOGNITION TRAINING EFFECTS ACROSS IDENTITIES

Dalili MN, School of Experimental Psychology, Univ of Bristol, 12a Priory Rd, Bristol, UK BS8 1TU, michael.dalili@bristol.ac.uk
Munafò MR(1), Penton-Voak IS(1) (1) 12a Priory Road, School of Exp Psyc, Univ of Bristol, BS8 1TU

Emotion recognition training tasks have shown promise in the modification of cognitive biases associated with mental health issues such as low mood (Penton-Voak et al., 2012, The British Journal of Psychiatry, 201, 71-72) and aggressive behaviour (Penton-Voak et al., 2013, Psychological Science, 24, 688-697). However, these emotion recognition training tasks use stimulus sets using a single prototypical face. Hence, the extent to which the lab training influences perception of emotion in other, non-trained faces is unknown. We investigated the generalisability of training effects when using prototypical faces by randomising 160 healthy adults (81 females) aged 18 to 39 to one of four training conditions in which they completed versions of the Bristol Emotion Recognition Training task. This task is designed to increase the perception of happiness over sadness in ambiguous facial expressions. Two of the conditions were stimulus-congruent, where participants saw the same stimulus set during baseline, training and test phases of the task, while the remaining two conditions were stimulus-incongruent, where participants responded to faces of the opposite gender during the test phase of the task. A paired-samples t test revealed training effects for both stimulus-congruent and stimulus-incongruent conditions (paired mean differences = -1.55 to -1.05, 95% CIs -2.01 to -0.47, p < .001) as participants identified more faces as happy rather than sad post-training. The mean thresholds at baseline were 7.29 (SD = 1.62) frames in the stimulus-congruent condition and 7.43 (SD = 1.63) frames in the stimulus-incongruent condition. The mean thresholds at test post-training were 8.84 (SD = 2.02) frames in the stimulus-congruent condition and 8.64 (SD = 2.11) frames in the stimulus-incongruent condition. Critically, independent samples t tests demonstrated the generalisability of these training effects across identities as participants responding to the same stimulus set responded similarly whether they were trained using the same set of faces or not (mean differences = -0.18 to 0.23, 95% CIs -1.14 to 1.11, p > .613). These findings indicate that emotion perception training using prototypical faces generalises well to non-trained faces. Therefore we expect that individuals who perceive more ambiguous faces as happy rather than sad post-training are likely to do so in natural settings. Funding for this study was provided by the Medical Research Council.
TA10

HARD AND SOFT ILLUSIONS OF CONTROL IN A NOVEL LABORATORY TASK

Tobias-Webb J, Dept of Experimental Psychology, Univ of Cambridge, Downing St, Cambridge CB2 3EB, jjt40@cam.ac.uk
Aitken MRF (1), Clark L (1) (1) Lab for Affect, Risk and Gambling Experiments, Dept of Psychology, Downing St, Cambridge CB2 3EB

Introduction: Sense of agency is distorted in several forms of mental illness and is linked to dopamine transmission in particular. One instance of distorted agency in gambling behavior is termed the Illusion of Control (IoC), describing a belief that one’s personal skills can influence outcomes under conditions of chance (Langer, 1975, J Pers Soc Psychol, 32, 311-328; Stefan & David, 2013, J Appl Soc Psychol, 43, 377-386). Past work has focused on subjective ratings of confidence or control as the key measure of IoC. In these studies, healthy participants express higher confidence when they have irrelevant control. However, to demonstrate an illusion, participants should actively disadvantage themselves (e.g. risk something of value) to implement control. We refer to these as ‘soft’ and ‘hard’ versions of IoC, respectively. Methods: We sought to develop a realistic gambling task to quantify IoC, where participants could ‘spin’ a circular arrangement of 13 cards to ‘find the ace’. We compared three conditions: a no control (NC) condition, a ‘Free Spin’ (FS) condition involving irrelevant control, and a condition where participants could Pay to Spin (PS), indicating hard IoC. Confidence ratings were taken on a trial-by-trial basis. Student participants (n = 78, 52.6% male) played 54 trials where the probabilities of winning and losing were also systematically varied. Results: Overall, 64% of participants paid at least once to move the wheel, with 28% paying on more than 5 (of 18) PS trials. Confidence ratings varied significantly across the three spin conditions, F = 5.58, p = .011, driven by higher ratings in both the FS (M = 29.09, SE = 2.65) and PS (M = 30.16, SE = 3.09) conditions compared to the NC condition (M = 25.20, SE = 2.33). No significant difference was found between FS and OTP. Participants who paid to spin in the PS condition had higher confidence in the FS condition (M = 28.96, SE = 2.12) than participants who did not (M = 20.39, SE = 2.71), F = 4.74, p = .033, implying that the two forms of IoC are related. Conclusions: As a group, student volunteers display both soft and hard definitions of IoC, actively disadvantage themselves to exercise illusory control over a game of chance. In ongoing work, we will use the task to examine IoC in gambling populations and with alcohol administration. Sources of financial sponsorship: Cambridge Australia Poynton International Scholarship

TA11

MAKING DECISIONS WHEN EMOTIONS RUN HIGH: A MODULATORY ROLE FOR TRAIT ANXIETY

Charpentier CJ, Inst of Cognitive Neuroscience, UCL, Alexandra House 17 Queen Square, London, WC1N 3AR, caroline.charpentier.11@ucl.ac.uk
Sim A(1), De Martino B(2), Sharot T(3), Roiser JP(1) (1) Inst of Cognitive Neuroscience, UCL, 17 Queen Square, London WC1N 3AR (2) Dept of Psychology, Univ of Cambridge (3) Dept of Cognitive, Perceptual, and Brain Science, UCL, 26 Bedford Way, WC1H 0AP

How we evaluate, judge, or choose things around us can be heavily influenced by our current emotional state. However, it is unclear how risky economic choices are modulated by incidental, task-irrelevant, emotional context. To investigate this question, we designed a novel behavioural paradigm, combined with functional magnetic resonance imaging (fMRI), in a sample of 28 healthy volunteers (15 males, 13 females, age range 19-47 years, mean 26.5) encompassing a varying range of trait anxiety symptoms, as measured by the State-Trait Anxiety Inventory. Participants completed a loss aversion task where each decision to accept or reject a gamble was preceded by emotional (happy faces, fearful faces) or non-emotional (neutral faces, objects) primes. To ensure participants processed the content of the primes without suspecting the purpose of the study or trying to voluntarily alter their choice behaviour, the gambling task was embedded in a working memory task. Participants’ loss aversion, or their tendency to overvalue potential monetary losses relative to equivalent gains, was modulated by the emotional context as a function of trait anxiety (negative correlation, R = -0.503, P = 0.006). In low anxious individuals (N=14 after median split, trait anxiety score range 20-30), both fearful and happy emotional face primes, relative to non-emotional stimuli, induced a significant increase in loss aversion (+4.98%, t(13)=3.16, P=0.008). By contrast, in high anxious individuals (N=14, trait anxiety score range 33-44) this effect was not present (t(13)=-1.46, P=0.17). This result suggests that individual levels of trait anxiety modulate the extent to which emotional context, independent of valence, interferes with risky economic decision-making. Functional neuroimaging analyses revealed an increased response to losses relative to gains in the ventral striatum, and the strength of this “neural loss aversion” signal was found to be negatively modulated by trait anxiety (R=-0.397, P=0.036). Functional connectivity analyses revealed that increased coupling between signal in this ventral striatum region during gamble and amygdala-prefrontal responses to emotional context predicted changes in behaviour. Taken together, these findings shed light on a novel potential mechanistic account underlying how economic decisions are modulated by emotion. In particular, the reduced sensitivity to pathological anxiety disorders in individuals with low trait anxiety may be driven by the engagement of adaptive harm-avoidance mechanisms in emotionally arousing contexts. Financial sponsorship: UCL Grand Challenge Studentship, Wellcome Trust.
TA12

THE EFFECTS OF ANTICIPATION OF LOSS ON ATTENTIONAL BIAS FOR REWARDING CUES

Jedras P. Dept of Psychological Sciences, Univ of Liverpool, Eleanor Rathbone Bldg, Bedford St South, Liverpool, L69 7ZA, p.s.jedras@liv.ac.uk
Field M. Dept of Psychological Sciences, Univ of Liverpool, Liverpool L69 7ZA

Introduction: The anticipation of reward plays an important role in addictive behaviours (Jones et al., 2012, QJEP, 65, 2333-2342). The results of a previous study revealed outcome-specific effects of reward expectancy on attentional bias for rewarding cues (Jedras et al 2013, Journal of Psychopharmacology, 27(Suppl. 8), A25). In this study we found that attention tended to be selectively allocated towards pictures of rewards which were anticipated to be available imminently: anticipation of chocolate increased the attentional bias only for chocolate related stimuli, whereas anticipation of alcohol increased the attentional bias only for alcohol related stimuli. Despite these clear effects of anticipation of reward on attentional bias for rewarding stimuli, it is unclear if anticipation of loss leads to similar increases in attentional bias for rewarding stimuli, or if loss anticipation prompts a decrease in attentional bias. This was the focus of the present study. Methods: Healthy participants ranging in age between 18 and 31 years (M=20.83, SD=3.51) consuming alcohol and chocolate on a regular basis (N=31 females, N=4 males) completed an eye tracking computer task to evaluate the effects of loss anticipation on attentional bias for alcohol and chocolate pictorial cues. During the task, on a trial-by-trial basis, they were informed about chances of losing (100%, 50%, 0%) chocolate or beer points. Immediately after receiving this information about the probability of loss of reward points, participants' eye movements to alcohol-related and chocolate-related pictures were measured. Results: Results indicated that participants showed an overall attentional bias for rewarding cues (relative to neutral cues) (F(1,34) = 10.072, p = .003, np2 = .229). However, repeated measures ANOVA revealed that this overall bias was not affected by the anticipation of loss (F(2, 68) = .067, p = .935, np2 = .002). Conclusions: Comparing the results of the current study with the findings of previous research it could be concluded that the anticipation of reward but not the anticipation of loss moderates attentional bias for rewarding cues. These findings advance our understanding of the moderators of attentional bias for reward-related cues, including the bias for alcohol cues that is thought to be an important feature of alcohol use disorders. Funded by a University of Liverpool PhD studentship.

TA13

ALCOHOL-RELATED AND NEGATIVELY-VALENCED CUES CAUSE DISINHIBITION IN SOCIAL DRINKERS

McGrath E. Inst of Psychology, Health & Society, Univ of Liverpool, 2.19 Eleanor Rathbone Bldg, Bedford St South, Liverpool, L69 7ZA, emcgrath@liv.ac.uk
Jones A, Field M. Eleanor Rathbone Bldg, Univ of Liverpool, Bedford St South, Liverpool, L69 7ZA

Introduction: Disinhibition, or the ability to stop, change or delay a behaviour that is no longer necessary or appropriate is a fundamental construct associated with heavy drinking. Recent hypotheses suggest that temporary fluctuations in disinhibition may promote alcohol seeking behaviour, and these fluctuations may be caused by exposure to alcohol-related cues. This research set out to examine whether social drinkers demonstrated increased disinhibition to alcohol-related cues, compared with general valenced cues. Methods: 64 participants (32 male) took part in a laboratory study consisting of a stimulus-irrelevant stop signal task with cues (positive, negative, alcohol and neutral) embedded. Valenced cues were chosen from the International Affective Picture System (IAPS) based on pilot ratings. Participants also provided estimates of fortnightly unit consumption, Alcohol Use Disorders Identification Task (AUDIT) scores and craving data. Results: There was a main effect of cue type on stop signal reaction time, a measure of disinhibition (F(3, 189)= 2.95, p<.05). Alcohol cues significantly increased disinhibition compared to both neutral (p<.05) and positive cues (p<.05), but not negative cues (p>.10). Negative cues significantly increased disinhibition compared to neutral cues (p<.05). Results were not influenced by drinking status (heavy versus light drinkers) or gender. Conclusions: Both negatively-valenced and alcohol-related cues led to temporary increases in disinhibition in social drinkers. These findings suggest that the arousing properties of cues, rather than the pictorial content, may influence disinhibition. The findings also support the hypothesis that disinhibition is a transient state influenced by environmental cues. Future research should aim to develop methods of reducing the impact of cues on disinhibited behaviour. Research was sponsored by the Medical Research Council.

TA14

A SYSTEMATIC REVIEW OF COGNITIVE TASKS SENSITIVE TO ACUTE ABSTINENCE AND PREDICTIVE OF CESSATION OUTCOME IN SMOKERS

Grabski MG, Exp. Psychology, Univ of Bristol, 5 Priory Rd, Bristol, UK, BS8 1TU, mgl3939@bristol.ac.uk
Curran V (1), Husbands S (2), Nutt D (3) Munafo M (4) (1) Clinical Psychopharmacology Unit, UCL, Gower St., London, WC1E 6BT (2) Dept of Pharmacy and Pharmacology, Univ of Bath, Claverton Down, Bath, BA2 7AY (3) Dept of Medicine, Imperial College, Burlington Danes Bldg, Du Cane Road, London, W12 0NN (4) School of Exp. Psychology, 12a Priory Road, Bristol BS8 1TU

Background: A better understanding of the underlying mechanisms of nicotine withdrawal is vital in order to develop novel behavioral and pharmacological treatment methods for smoking cessation (Baker et al., 2004, Psychological Review, 111 (1), 33-51; Hughes, 2006, Nicotine & Tobacco Research, 8 (2), 153-156). Insights from laboratory paradigms could be a cost- and time-effective way of guiding these developments, if performance on these tasks is modulated by short-term abstinence and is also related to long-term cessation outcomes. A comparison of performance after a period of acute abstinence with performance in a smoking-satiated state should indicate cognitive functions affected by nicotine withdrawal in regular smokers (Leventhal et al., 2010, Addictive Behaviors, 35, 1120-1130). Furthermore, as severity of withdrawal has been related to
cessation outcomes, it is feasible that cognitive performance predicts long-term cessation outcomes (West et al., 1989, Psychological Medicine, 19 (4), 981-985). Testing cognitive performance before a cessation attempt could provide evidence for this, and indicate whether the underlying cognitive functions predictive of outcome are consistent with those sensitive to acute abstinence. Therefore, we conducted a systematic review investigating: a) which cognitive tasks are most sensitive to acute abstinence in smokers, and b) which cognitive tasks are predictive of smoking cessation outcome. Methods: For both questions, the databases Embase, MedLine, Web of Science and Psychnfo were searched. Searches were limited to peer reviewed journal articles written in English and involving healthy volunteers. Results: The initial search revealed 2,673 studies relevant to acute abstinence and 11,459 relevant to cessation. These were evaluated using a pre-defined set of inclusion and exclusion criteria for each topic, resulting in 31 studies for inclusion relevant to acute abstinence and 9 studies relevant to cessation. Cognitive domains investigated predominately included, for acute abstinence, selective attention, working memory and attention, and, for cessation, attention. Results: from those tasks used at least three times (Dot Probe, Regular Stroop, Smoking Stroop, Mental Arithmetic, Recognition Memory, Delay Discounting in acute abstinence studies) were meta-analyzed. Effects sizes indicated an effect of acute abstinence for Mental Arithmetic (ES= 0.81, 95% CIs 0.47, 1.15), Delay Discounting (ES= 0.39, 95% CIs 0.04, 0.74), and Recognition Memory (ES= -0.81, 95% CIs 0.03, 1.60). Conclusions: Several tasks seemed to be affected by acute abstinence, but as the number of studies was low results should be interpreted with caution. Interestingly none of the tasks designed to measure selective attention in smokers showed any effect. Summarizing the evidence from the review and the meta analysis it seems that, despite being the main focus, attentional reaction time tasks might not be the best way to investigate acute abstinence, and instead delay discounting and memory tasks might yield more robust results. Funding: This project is funded by an ESRC PhD studentship with co-funding from Rusan Pharma Ltd.

TA15

EPISODIC FUTURE THINKING IMPAIRMENT IN LONG TERM OPIATE USERS

Mercuri K, The Australian Catholic Univ, Level 5, The Daniel Mannix Bldg, Young St, Fitzroy, Victoria, Australia, 3065, kim.mercuri@acu.edu.au
Terrett G(1), Henry JD(2), Bailey PE(3), Curran V(4), Rendell PG(1) (1) The Daniel Mannix Bldg, The Australian Catholic Univ, Fitzroy, Victoria, Australia (2) McElwain Bldg, The Univ of Queensland, St Lucia, QLD Australia (3) Psychology Bldg, School of Social Sciences and Psychology, Univ of Western Sydney, Bankstown, NSW, Australia (4) Clinical Psychopharmacology Unit, University College London, London, UK

There is considerable literature showing that opiate use is associated with a range of neurocognitive deficits, including deficits in executive control and episodic memory. However, no study to date has assessed whether these neurocognitive difficulties extend to the ability to mentally time travel into one’s personal future. This is a surprising omission given that executive control and episodic memory are considered to be critical to engage episodic foresight. In addition, opiate-related brain changes have been identified in the neural regions that underlie the capacity for episodic foresight. In the present study, we therefore assessed how episodic foresight is affected in the context of chronic opiate use, as well as the degree to which any observed deficits are related to more general difficulties with executive control and episodic memory. Forty eight long-term heroin users enrolled in an opiate substitution program, and 48 controls with no previous history of substance dependence were tested. The results showed that, relative to controls, the clinical group exhibited significant impairment in episodic foresight (assessed with adapted version of Autobiographical Interview), but did not differ in their capacity for executive control or episodic memory. These data provide important preliminary evidence that episodic foresight might be particularly susceptible to the neurocognitive effects of opiate use, as the difficulties identified were not simply secondary to more general executive control or episodic memory impairment. The practical and theoretical implications of these data in relation to the treatment of substance dependence disorders are discussed. This project was financially supported by student grants provided by the Faculty of Art and Sciences at the Australian Catholic University.

TA16

APATHY, VENTRICULOMEGALY AND NEUROCOGNITIVE IMPROVEMENT FOLLOWING SHUNT SURGERY IN NORMAL PRESSURE HYDROCEPHALUS

Peterson KA, Dept Psychiatry, Univ of Cambridge, Box 189 Level 4 Psychiatry Addenbrooke’s Hosp, Hills Rd Cambridge, CB2 0QQ, kap45@medschl.cam.ac.uk
Housden CR(1), Killikelly C(1), DeVito EE(1,2), Keong NC(2), Savulich G(1), Czosnyka Z(2), Pickard JD(2), Sahakian BJ(1,3) (1) Dept Psychiatry, Univ of Cambridge, Addenbrooke’s Hosp, Cambridge CB2 0QQ (2) Dept Neurosurgery, Univ of Cambridge, Addenbrooke’s Hosp, Cambridge CB2 0QQ (3) MRC/Wellcome Trust BCNI, Univ of Cambridge, Cambridge CB2 3EB

Introduction: Apathy - impaired motivation and goal-directed behaviour - is a common yet often overlooked symptom in normal pressure hydrocephalus (NPH). Caudate atrophy often yields apathetic symptoms however this structural and functional relationship has not yet been explored in NPH. Additionally, little is known about the relationship between apathy and post-shunt cognitive recovery. Methods: This audit investigated whether apathetic symptoms improve following shunt surgery in NPH, and whether this relates to cognitive response. In addition, we assessed the utility of the bicaudate ratio as a measure of ventriculomegaly. Twenty-two patients with NPH completed the Mini-Mental State Examination, the Apathy Evaluation Scale and the Geriatric Depression Scale before and 3 to 9 months after shunt surgery. Preoperative ventriculomegaly was related to apathy. Results: Greater preoperative ventriculomegaly was associated with increased level of apathy and depression. A reduction in apathetic symptoms following shunt surgery was associated with improved performance on the Mini Mental State Examination. Conclusions: Apathy may be indicative of a greater degree of subcortical atrophy in NPH and shunt surgery may improve motivational as well as cognitive and physical symptoms. Funding: KAP was funded by NIHR Biomedical Research Centre (Neurosciences Theme). CK and GS were funded by a grant to BJS from Janssen, J&J. EED was funded by a grant from Rusan Pharma Ltd.
THE ASSOCIATION BETWEEN DISPOSITIONAL MINDFULNESS AND THE PERCEPTION OF EMOTIONAL FACES

**Ainsworth B**, Dept Psychiatry, Univ Southampton, Academic Centre, 4-12 Terminus Terrace, Southampton, SO14 3DT, ben.ainsworth@southampton.ac.uk

Eddershaw R(1), Meron D(2), Baldwin DS(2,3) Garner M(1,2) (1)Psychology, Uni. Southampton, Southampton, SO17 IBJ; (2)Clinical and Experimental Sciences, Uni. Southampton, 4-12 Terminus Terrace, Southampton, SO14 3DT. (3)Dept of Psychiatry, Uni. of Cape Town, Cape Town, South Africa

Introduction: Recent neurocognitive accounts of mindfulness suggest that mindfulness can protect against/correct maladaptive biases in cognition and emotion that characterize anxiety. We have previously shown that trait mindfulness is associated with improved executive attention control (Ainsworth B, Eddershaw R, Meron D, Baldwin DS, Garner M. (2013). The effect of focused attention and open monitoring meditation on attention network function in healthy volunteers. Psychiatry Research, 1226–1231). Here we examine the relationship between mindfulness, mood and anxiety, and performance on a facial emotion-recognition task. Method: 76 healthy volunteers (M=20.3 years, SD=4.1) were asked to classify the emotion of computer-manipulated ambiguous facial expressions that varied in emotion (anger/happiness/sadness/neutral), and intensity (25%/50%/75%). Participants’ sensitivity to detecting emotion was measured over 120 trials (12 presentations of 10 conditions). Participants also completed self-report measures of mindfulness, anxiety and mood. Results: Sensitivity to emotion was computed by comparing ‘hits’ (correctly identify expressed emotion) with ‘false alarms’ (incorrectly perceiving an alternative emotion). Correlations between self-report scores and sensitivity were examined. Lower mood and increased anxiety were associated with reduced sensitivity for positive emotion (r=-.27, p=.014). Increased mindfulness was associated with increased sensitivity towards subtle (25%) positive emotions (r=.29, p=.009). Further analysis of this association found that increased mindfulness was associated with more ‘hits’ (r=.30, p=.007), but not ‘false alarms’. Mindfulness was not associated with any response biases towards specific emotions (r=.10, p=.37). Discussion: Our study is the first to examine the association between dispositional mindfulness and emotion-processing. Our findings are in line with notions that awareness of the present moment and non-judgemental acceptance (while maintaining ‘non-biased’ and objective awareness, as cultivated by mindfulness training) increase sensitivity to affective cues, leading to enhanced emotion regulation and increased wellbeing. This work was funded by an MRC-ESRC Grant: ES/H018514/1 awarded to M Garner, B Ainsworth, P Chadwick and D Baldwin.

LSD SELECTIVELY ENHANCES SUGGESTIBILITY BUT NOT CUED IMAGINATION IN HEALTHY VOLUNTEERS

**Carhart-Harris RL**, Centre for Neuropsychopharmacology, Imperial College London, Burlington Danes Bldg, Hammersmith Campus, 160 Du Cane Rd, London, W12 ONN r.carhart-harris@imperial.ac.uk

Kaelen M(1), Bolstridge M(1), Feilding A(2), Nutt DJ(1) (1) Imperial College London, Centre for Neuropsychopharmacology, Div of Brain Sciences, Faculty of Medicine, London, UK (2) The Beckley Foundation, Beckley Park, Oxford, UK

Background: LSD has a history of use as a psychotherapeutic aid in the treatment of mood disorders and addiction. At least one study has demonstrated enhanced suggestibility under LSD and the aim of the present study was to test the reliability and specificity of this effect in a modern research study. Methods: Ten healthy volunteers were recruited (1 female, mean age = 34.2 ± 7.4) all of whom had at least one previous experience with a classic psychedelic drug (mean LSD uses = 65 ± 90, range = 0 - 250) but not within 21 days of the study. LSD was administered via intravenous infusion (40-80µg in 10ml saline) over 3 minutes in a single-blind, within-subjects, placebo-controlled design. Suggestibility and cued imagination were assessed using two validated methodologies: the Creative Imagination Scale (CIS) and the Questionnaire upon Mental Imagery (QMI) respectively. The CIS examines suggestibility via experimenter-read descriptions of detailed scenarios (e.g. a 220 word description of the sensation of heat on the hand) and subsequent participant-ratings of the vividness and realism of the suggested experience (rated 0-4, 4 = “almost exactly the same [as experiencing in reality]”). The QMI assesses the vividness of cued mental imagery (e.g. “imagine a green traffic light”) rated via a 0-6 scale (6 = “very vivid and as clear and as in reality”). CIS and QMI items were binarised into two versions (A & B), balanced for “efficacy” (i.e. A = B) and then counterbalanced across conditions (i.e. 50% ‘A’ under LSD). The QMI and CIS were issued 140 and 210 minutes post-infusion respectively, corresponding with the peak intensity of the drug’s subjective effects. Results: Volunteers gave significantly higher ratings on the CIS after LSD than placebo (LSD = 2.9 ± 1.3, placebo = 1.8 ± .7; p = .02, 2-tailed, paired t-test) but not on the QMI (LSD = 4.3 ± 1.3, placebo = 3.7 ± 0.8, p = .01, 2-tailed, paired t-test). Conclusions: These results imply that the influence of detailed suggestions is greater under LSD but cued imagination, which demands the rapid focus of attention, is not significantly modulated by the drug. Enhanced suggestion under LSD may have implications for its use as an adjunct to psychotherapy, where suggestion plays a significant role. Moreover, the results imply that LSD only enhances suggestibility when the suggestions are of a sufficient duration and level of detail. Funding: Financial support was received from the Beckley Foundation for this work.
TA19

THE EFFECTS OF ALCOHOL HANGOVER ON DRIVING, PERCEIVED WORKLOAD AND MOOD DURING A 20 MINUTE SIMULATED ‘COMMUTE TO WORK’

Alford C, Health and Social Sciences, Univ of the West of England, Coldharbour Lane, Bristol, BS16 1QY, chris.alford@uwe.ac.uk

Lands S, Univ of the West of England, Coldharbour Lane, Bristol BS16 1QY

Introduction – There have been relatively few studies investigating the effect of alcohol hangover on driving performance next day when participants are experiencing a hangover following evening alcohol consumption. Although drivers may be able to briefly compensate for a known impairment, (Verster and Roth 2012 Accident Analysis & Prevention, 2013, 58: 244-248) the effects on a typical ‘commute to work’ in a demanding environment have not been investigated. Methods – Nineteen participants (mean age 20.2 years, 13 female) who were driving license holders underwent a 20 minute drive with a speed limit set to 50mph and including a mixed urban and rural environment which included hazards (e.g. pedestrian stepping into the road), and concomitant divided attention task (spotting change between triangle/diamond peripheral stimuli) with the STISIM driving simulator. A counterbalanced treatment order was employed (hangover/no-hangover), with measures including STISIM driving performance variables together with mood (Bond and Lader VAS), subjective hangover (Penning Hangover rating scale) and perceived workload (NASA TLX).

Results – Hangover was substantiated by hangover ratings (e.g. fatigue, apathy, poor concentration, confusion, clumsiness, thirst) being greater than previously reported (Penning et al 2013 Psychopharmacology, 225, 803-810). Significant findings (P<0.05) reflecting impaired vehicle control included increased speed variability (>20%) as well as reaction time (>30%) to peripheral stimuli in the hangover condition. Possible lapses were shown with doubling the number of lane excursions and (>30%) increased time spent over the centre line. A further analysis removed participants with residual alcohol (mean BAC <0.05%), with differences remaining significant apart from speed variability that reduced to a trend (P=0.08). In the hangover condition overall negative mood was significantly increased with average scores increasing from 30 to 59 where 100 is maximum negative score. Four of 6 subjective workload parameters were significantly increased reflecting greater effort and increased mental demands.

Conclusions – Whilst driving impairment with alcohol hangover has recently been reported during a simulated 1 hour highway drive (Verster et al 2014 Psychopharmacology, DOI 10.1007/s00213-014-3474-9), the significant impairments seen here, with only a relatively short driving duration reflecting a typical commute to work, and using a more mentally demanding driving environment, represents a new finding. The results suggest that in a demanding driving environment even shorter driving periods are detrimentally affected, and that drivers were unable to compensate despite increased subjective effort. These findings could be incorporated into driver safety campaigns. No financial sponsorship was received for this study.

TA20

COGNITION IN PREGNANCY: EFFECTS OF DEPRESSION

Bulage GB, Dept of Psychological Medicine, Inst of Psychiatry UK, 16 De Crespigny Park, London, SE5 8AF, gloria.bulage@kcl.ac.uk

Pawlbys, Conroy S, Parriante CM. Perinatal Psychiatry, Dept of Psychological Medicine, Inst of Psychiatry UK

Introduction: Depression can have negative cognitive symptoms including deficits in problem-solving abilities and concentration and memory (Marazziti et al., 2010; Doumas et al., 2012). This study compares the cognitive abilities of pregnant women currently depressed with those not depressed. Methods: This study is part of an on-going longitudinal study, Psychiatry Research and Motherhood (PRAM). Women were recruited from the antenatal clinics and perinatal psychiatry services of a large London hospital and visited in their homes between 25-30 weeks gestation. Their mental health was assessed using the SCID and diagnoses of current major depressive disorder (DSM-IV) were made (N=32). Thirty seven women with no current diagnosis form the comparison group. Demographic details were collected. A series of psychometric instruments (Wechsler scales) were administered to assess the women’s current and premorbid cognitive levels including Full Scale IQ, Logical Memory and Digit Span and the Wechsler Test of Adult Reading (WTAR). Results: Initial analyses revealed no significant differences in the IQ, Logical Memory, Digit Span or WTAR scores of the pregnant women who were depressed and those who were not depressed. Highly significant findings were however found in the scores of women depending on their level of education. Compared with women without a higher level qualification, women who had a degree/diploma scored significantly higher on all the cognitive measures (IQ, t(67)=6.38, p<.001; Logical Memory Recall, t(47)=4.95, p<.001; Logical Memory Delayed Recall, t(64)=4.94, p<.001; WTAR, t(67)=4.53, p<.001) except Digit Span (t(66)=1.59, p<.12. There was also no significant difference between the current IQ scores of women with and without higher qualifications and their premorbid WTAR scores (t(64)=0.65, p=0.52). In a multivariate analysis the effect of the woman’s higher educational qualification remained a significant predictor of her current and premorbid level of cognitive functioning, except in relation to digit span where there was a significant effect of the woman’s depression (F(1) = 4.47, p = 0.04) but not of her qualifications. Conclusion: The finding that compared to pregnant women who were not depressed, those who were depressed, irrespective of educational qualifications, have lower scores on Digit Span, a measure of non-linguistic short-term memory gives some support to the hypothesis that depression has a negative effect on a woman’s cognitive non-linguistic abilities in pregnancy. Differences were not found for the other measures of general cognitive abilities and of linguistic memory, nor did we find a difference in the women’s current IQ compared with their premorbid IQ.

Funding: Foundation for the Study of Infant Death; South London Clinical Research Network Contingency Funding
TA21

ARE THERE GENDER DIFFERENCES IN NEUROCOGNITIVE FUNCTIONS OF PATIENTS WITH OBSESSIVE-COMPULSIVE DISORDER?

*Kaser M* Dept of Psychiatry, Univ of Cambridge, Level 4, Box 189, Addenbrooke’s Hospital, CB2 2QQ, mk708@cam.ac.uk
Hacioglu M (1) Yildirim EA (1) Saatcioglu IO (1) (1) Bakirkoy Research and Training Hospital for Psychiatry, Neurology and Neurosurgery, Istanbul, Turkey

Introduction: Patients with obsessive-compulsive disorder (OCD) have neurocognitive impairments in various domains. The factors associated with the neurocognitive dysfunction are yet to be elucidated. Although there have been reports indicating sex-related clinical differences such as age of onset, frequency of specific symptoms, only few studies compared the neuropsychological performance in male and female patients with OCD (Mataix-Cols et al. 2006, Applied Neuropsychology 13.1:42-50, Segalas et al. 2010, Comprehensive Psychiatry 51.3:303-311). In this study, we aimed to investigate whether there are gender-specific differences in neurocognitive functions of patients with OCD. Method: 70 patients (39 female, 31 male) matched for age and education and meeting DSM-IV diagnostic criteria for OCD were enrolled in the study. A neuropsychological battery comprised of Continuous Performance Test, Stroop Test, Wisconsin Card Sorting Test, Digit Span, and Iowa Gambling Task was used. Patients were assessed for OCD symptom severity (Y-BOCS), depression (Hamilton Depression Scale), and anxiety levels (State and Trait Anxiety Inventory).

Results: Age of onset, symptom severity, depression and anxiety levels were comparable between female and male OCD patients. Independent sample statistical analysis showed that there were no significant differences in any of the neuropsychological test measures between groups (p>0.05). Regression analysis revealed that Y-BOCS scores did not have mediator effects on the neuropsychological performance (R=0.22, Standard Error of the Estimate=5.732).

Conclusion: The results from this well-matched study sample indicated that male and female patients with OCD showed no difference in multiple domains of neurocognitive function, including attention, working memory, executive functions and decision-making. These results are in line with the previous studies that reported the lack of gender specific differences at cognitive domains related to fronto-striatal circuitry. Dr Muzaffer Kaser is supported by Cambridge-IDB International Scholarship and receives financial support from his affiliated university, Bahcesehir University, Istanbul, Turkey.

TB01

ROLE OF ALPHA-5 SUBTYPE OF NICOTINIC ACETYLCHOLINE RECEPTORS IN AVERSIVE AND DISCRIMINATIVE STIMULUS PROPERTIES OF NICOTINE

*Michaud DR* Inst of Neuroscience, Newcastle Univ, Newcastle, NE2 4HH d.r.michaud@newcastle.ac.uk
Ifitikhar W (1) Maskos U (2), Shoab M (1) (1)IoN, Newcastle Univ, Newcastle, NE2 4HH, (2)Pasteur Inst, 25-28 Rue du Docteur Roux, 75015 Paris, France

Nicotine addiction is a prominent issue for tobacco users, and research suggests that the alpha-5 subunit on the nicotinic acetylcholine receptor (nAChR) and its polymorphisms play an important role in the high frequency of nicotine use. To further elucidate the role of the α5 nAChR subunit, we compared wild type mice with α5 knock-out mice in a conditioned place aversion procedure with nicotine and examined nicotine as a discriminative stimulus in a two-lever operant conditioning task. Conditioned place aversions were established following vehicle and nicotine (0.15, 0.5 and 1.5 mg/kg SC) conditioning sessions in WT and α5-/- groups. Wild-type and α5-/- mice were trained using a two lever nicotine discrimination task in two training doses (0.75 and 1.5mg/kg SC, 10 min pre-session interval). Once mice reached the 80% acquisition criterion, they were tested with graded doses of nicotine in a randomized order. Furthermore, to characterise the pharmacology of the nicotine discrimination, tests with nAChR agonists and antagonists were also conducted. Compared to WT mice that exhibited dose-related place aversions in response to nicotine (P<0.05), the α5 KO failed to show any form of aversion. In the nicotine discrimination task, mice trained on 1.5mg/kg dose of nicotine acquired discrimination faster compared to the 0.75mg/kg dose in both the WT and KO groups of mice. There was no statistical difference on acquisition between the WT and KO groups. These data demonstrate that the α5 nAChR subunit plays a role in the aversive stimulus properties of nicotine, which is in agreement with published literature, suggesting the α5 nAChR subtype regulates nicotine intake. Despite this difference, the α5 subtype plays a lesser role in the transduction of the subjective effects of the large dose of nicotine (1.5mg/kg), although the possibility remains that other nAChR subtypes may also contribute. Further studies will investigate the pharmacological nature of the nicotine discrimination between the wild-type and α5 KO mice. Research supported by Newcastle University and the Pasteur Institute, France.

TB02

ICSS PATTERNS OF RESPONDING TO RATS AFTER ANTAGONISM OF GHRELIN RECEPTORS

*Wellman P* Psychology and Neuroscience Texas A&M Univ, Room 248 Psyc MS 4235 College Station,TX, 77843-4235, paul-wellman@tamu.edu
Rodriguez J(1), Clifford SP(1) (1) Dept of Psychology, TAMU, College Station, TX 77843-4235

Ghrelin receptors (GHR-Rs) located on dopamine neurons within the ventral tegmental area modulate the behavioral and reinforcing actions of psychostimulants (Wellman, et al., Frontiers in Neuroscience, 2013, 171, 1-12). antagonism of GHR-Rs diminishes the development of locomotor sensitization to cocaine as well as to nicotine and diminishes the capacity of these psychostimulants to induce conditioned place preference. In the present study, we examine the impact of the GHR-R antagonist JMV 2959 and of nicotine on patterns of operant responding for low-level electrical intracranial self- stimulation (ICSS) of the lateral hypothalamus (LH). Adult male rats were implanted with LH electrodes and shaped to press for ICSS using a rate-frequency procedure. Treatments given were vehicle, 0.4 mg/kg NIC (i.p.) 6 mg/kg JMV 2959 (i.p.), and combination injections of 6 mg/kg JMV 2959 plus 0.4 mg/kg NIC . Relative to the rate-frequency curve evident after vehicle treatment, rats injected with 0.4 mg/kg NIC exhibited a significant increase in maximal rate of responding and a leftward shift of the rate-frequency curve, as would be expected
of a psychostimulant. While JMV 2959 alone did not reliably alter ICSS patterns, pretreatment with JMV 2959 produced a pronounced rightward and downward shift in ICSS responding. These results confirm our earlier observations in which JMV 2959 prevents the induction of locomotor sensitization to NIC (Wellman et al., Regulatory Peptides, 172, 77-80) and suppresses intravenous self-administration of NIC (Clifford, et al., SFN abstract, 2012). Collectively, these results argue that nicotine-induced reinforcement requires functional GHR-Rs and provide further evidence that ablation of GHR-R function may be a useful therapeutic approach to diminish the behavioral and reinforcing action of nicotine. The issue of weight regain associated with nicotine cessation is also of consideration in that antagonism of GHR-Rs may diminish appetite and weight regain evident after smoking cessation. The research presented within this abstract was supported by funds provided by the College of Liberal Arts, Texas A&M Univer

TB03

THE EFFECT OF THE Α7 NICOTINIC RECEPTOR ON MORPHINE CONDITIONED PLACE PREFERENCE IN MICE

Wright VL, Dept of Biology and Biochemistry, Univ of Bath, 0.40 4S Bldgs Claverton Down, Bath, BA2 7AY, vwl21@bath.ac.uk
Bailey CP (1) Wonnacott S (2) Heal DJ (3) (1) Dept of Pharmacy and Pharmacology, Univ of Bath, BA2 7AY (2) Dept of Biology and Biochemistry, Univ of Bath, BA2 7AY (3) RenSci, Pennyfoot St, Nottingham, NG1 1GF, UK

Cue associated learning plays an important role in motivation for rewards. This is necessary for survival, but can lead to drug addiction. Relapse to drug use can be triggered by re-exposure to drug-associated cues. Recently, nicotinic acetylcholine receptors (nAChRs) have been implicated in modulating responses to drugs of abuse other than nicotine (Feng et al (2011) Behav Brain Res 220:100-5). We have investigated the role of α7 nAChRs in morphine-primed learning, using conditioned place preference (CPP). We used methyllycaconitine (MLA), an α7 selective nAChR antagonist, to explore the effect of the α7 nAChRs on the acquisition, reconsolidation and reinstatement of morphine-CPP. 7-8 week old male C57BL/6J mice were used in an unbiased CPP protocol. Three experiments were performed. 1. Acquisition: animals received either MLA (4mg/kg, s.c.) or saline (10ml/kg/s.c.) 20 mins prior to morphine (10mg/kg, i.p.) or saline conditioning dose. 2. Reconsolidation: all animals were conditioned to morphine (10mg/kg, i.p.), 5 days after conditioning, animals were allocated one of two groups, both received one further conditioning trial (morphine, 10mg/kg, i.p.) and immediately after received either MLA (4mg/kg, s.c.) or saline (10ml/kg), followed by a CPP trial 1 day later. 3. Reinstatement: all animals were conditioned to morphine (10mg/kg, i.p.) then CPP was extinguished by repeated saline injections. Twenty mins prior to morphine reinstatement (5mg/kg, i.p.) animals received either saline (10ml/kg s.c.) or MLA (4mg/kg, s.c.). Time spent in drug-paired environment (15 minute test session) was measured. Data were analysed using In-vivo stat with a 2-way repeated measures mixed model ANOVA with Bonferroni’s correction for multiple comparisons. Morphine produced a robust CPP. MLA had no effect on the acquisition (control: 532.1±17.3, MLA: 539.9±22.9 s, p=0.69 n=16/treatment) or reconsolidation (control: 548.6±32.6, MLA: 549.4±25.6 s, p=0.981, n=12/treatment) of morphine-CPP. However, while the control morphine-primed group showed significant reinstatement (571±39 s post-reinstatement vs. 468±14 s at extinction, p=0.005, n=19), the MLA-treated group did not significantly restate (528±37 s post-reinstatement vs. 465±12 s at extinction, p=0.125, n=20). Comparison of time spent in the drug-paired environment after saline and MLA were not significantly different. Our findings suggest that α7 nAChRs may contribute to controlling reinstatement to morphine-CPP, with no effect on acquisition and reconsolidation. Experiments to determine the effect of activation of the alpha7 nAChR are on going, as well as biochemical experiments to investigate the mechanism. This work is supported by a grant from BBSRC industrial CASE award with RenSci, Nottingham, UK.

TB04

EXERCISE EFFECTS ON ALCOHOL DRINKING IN RATS: DIFFERENTIAL EFFECTS OF STRAIN

Mitchell SH, Behavioral Neuroscience, Oregon Health & Science Univ, 3181 SW Sam Jackson Park Road, Portland OR USA, 97239, mitchesu@ohsu.edu
Bard KA Dept of Behavioral Neuroscience, OHSU, 3181 SW Sam Jackson Park Road, Portland OR 97239 USA

Introduction: Some published data from the substance abuse recovery literature promote exercise as a means to speed recovery and recent pre-clinical studies using rats are consistent with that recovery literature, that is, wheel-running exercise in ethanol-dependent animals reduced susceptibility to ethanol-withdrawal seizures. Survey data also suggest that higher levels of exercise might be associated with lower levels of drug consumption, including alcohol, and that the reinforcing efficacy of drugs and drug-related cues may be diminished by exercise. However, no preclinical studies examining the causal relationship between concurrent exercise and alcohol consumption have been undertaken. Accordingly, we examined whether alcohol drinking varied as a function of exercise in two strains of rats reported to differ in baseline propensity to consume alcohol. Methods: Singly-housed, free-feeding adult male Fisher 344 and Lewis rats participated. Following baseline assessment of water and ethanol (10%) preference using a two-bottle choice procedure, animals were randomly assigned to an exercise (24-h access to a running wheel) or no-exercise group (no wheel available). A series of conditions were examined in which ethanol drinking was assessed when water was available and when unavailable, and when wheels were locked or free-running in the exercise group. Amounts of wheel running were also assessed. Results: Analyses of variance (ANOVA) techniques indicated that water consumption declined significantly in both strains over the course of the experiment (p<0.01), with no differences in the extent of decline as a function of exercise group (interaction: ns). Ethanol consumption increased over the same period (p<0.05), but subsequent ANOVAs indicated that these increases were driven primarily by consumption in the exercising Lewis rats (p<0.001), and tended to be correlated with the actual amount of exercise that individuals performed (p<0.10). Fischer rats exhibited similar patterns but increases in the exercise group were trends (p<0.10). These increases in ethanol consumption were especially marked in conditions when only ethanol was available. Conclusions: Exercise was associated with augmented alcohol drinking, though this effect appeared genetically moderated. Future work should examine the physiological processes underlying these effects and whether these effects can be attributed to a diminution of the reinforcing effects of alcohol, suggesting that more prolonged exercise might result in reduced drinking. Financial support: P60 10760 (Component PI: Mitchell)
TB05

ALCOHOL-PREFERRING P AND NON-PREFERRING NP RATS DO NOT DIFFER IN MOTOR IMPULSIVITY BUT DISPLAY MARKED DIFFERENCES IN GOAL/SIGN TRACKING BEHAVIOUR

Peña-Oliver Y, Psychology, Univ of Cambridge, Downing St, Cambridge, UK, CB2 3EB, yp249@cam.ac.uk

Giuliano C(1), Economidou D(1), Goodlett C(2), Dalley J(1) and Everett B(1) 1) Behavioural and Clinical Research Inst, Dept of Psychology, Univ of Cambridge, Downing Street, Cambridge, CB2 3EB, UK 2) Dept of Psychology, Indiana Univ-Purdue Univ Indianapolis, Indianapolis IN 46202

Alcohol addiction is often associated with high levels of impulsivity. In order to study this relationship and in particular that impulsivity predicts the propensity to drink alcohol, we have studied re-derived alcohol-preferring (P) and alcohol non-preferring (NP) rats, which have been selectively bred for their differential levels of ethanol preference, in the 5-choice serial reaction time task (5-CSRTT), a test that measures attention and impulsivity in rodents. P and NP rats were also tested in the Elevated Plus Maze (EPM) to explore individual differences in anxiety, and in an autoshaping task to measure sign and goal tracking behaviour. Drug-naive P and NP rats showed similar levels of impulsivity (premature responses) during baseline and the three long inter-trial interval sessions in the 5-CSRTT (the repeated measures ANOVA showed no significant session x strain interaction: F(14,364)=0.552, p=0.723; and failed to show any main effect of strain: F(1,26)=0.062, p=0.805). The P rats showed high levels of perseverative nose-poking in the food delivery magazine when compared to NP rats: main strain effect in the ANOVA for magazine head entries (F(1,26)=4.960, p<0.05) and time nose-poking in magazine (F(1,26)=11.692, p<0.01). Further exploration of this goal-oriented behaviour in an autoshaping task revealed that P rats showed higher levels of goal-tracking responses (higher number of magazine nose-pokes during CS presentations) in comparison to NP rats (F(1,26)=6.189, p<0.05), which showed higher levels of autoshaping (sign-tracking) behaviour (F(1,26)=6.189, p<0.05). P rats displayed higher levels of anxiety when compared to NP rats, as they showed reduced entries (F(1,28)=4.656, p<0.05) and time spent (F(1,28)=4.331, p<0.05) in the open arms of the EPM. The present results indicate that high ethanol drinking P rats when assessed prior to any alcohol drinking experience did not show high impulsivity, failed to develop a sign-tracking response, instead showing high goal-tracking behaviour and high levels of anxiety. This study was funded by a Medical Research Council Grant (G1002231).

TB06

REPEATED WITHDRAWAL FROM ETHANOL ON 5-CSRTT PERFORMANCE: MOUSE AND HUMAN FINDINGS

Sanchez-Roige S, School of Psychology, Univ of Sussex, Falmer, Brighton, BN1 9QG ss591@sussex.ac.uk

Baro V (1), Ellis-Pridgeon S (1), Trick L (1), Ripley TL (1), Stephens DN (1), Duka T (1) (1) School of Psychology, Univ of Sussex, Brighton BN1 9QG

There are well-established links between impulsivity and alcohol use in humans and animal models; but there are few studies using comparable methods to measure impulsivity in the two species. We developed a novel, iPad-based task to assess motor impulsivity and attentional abilities in humans, the human Sussex 5-CSRTT (Sx-5CSRTT), which is modelled on the 5-CSRTT in rodents (Robbins, 2002, Psychopharmacology, 93, 237-247). Adolescent (18-25 years) binge and non-binge drinkers, identified through the scores from the Alcohol Use Questionnaire (AUQ), completed the mouse adolescence (n=16) disrupted waiting impulsivity and attentional abilities in the rodent 5-CSRTT, revealed by the increased omission rates (F(1,31)=9.742, p<0.01, long ITI challenge) and premature responding (F(1,31)=6.047, p<0.05; vITI challenge) compared to CON mice (n=16). The ethanol-preferring C57BL/6J mice were also more impulsive during challenging conditions (F(1,31)=5.242, p<0.05, long ITI) in comparison to DBA/2J mice. Thus, in homologous measures in animal and human studies, premature responding and rates of omission were more evident both in young human social binge drinkers and the ethanol preferring C57BL/6J strain of mice; IEE during late adolescence also impaired waiting impulsivity irrespective of strain. Acknowledgements: This study was supported by the European Commission InterReg project “AlcoBinge”. The AlcoBinge project was selected within the context of the European programme of crossborder cooperation Interreg IV A France (Channel) – England, co financed by ERDF.
TB07

CHARACTERISING STRIATAL EFFECTS OF DOPAMINE 1- AND DOPAMINE 2-RECEPTOR SPECIFIC Α4 GABAA R KNOCKOUT NEURONS

Bailey JC, Psychology, Univ of Sussex, Brighton, UK, BN1 9QG, jcb40@sussex.ac.uk
Macpherson T(1), Robertson JM(1), Stephens DN(1), King SL(1) (1) School of Psychology, Univ of Sussex, Brighton, BN1 9QG, UK

Extrasynaptic GABAA receptors (GABAARs), present on medium spiny neurons (MSNs) which comprise 95% of nucleus accumbens (NAc) neurons, modulate effects of cocaine on reward-associated behaviours. These GABAA Rs, composed of α4, β and δ subunits, mediate a tonic inhibition which impacts the excitability of NAc MSNs. Approximately 50% of NAc MSNs contain Dopamine 1 receptors (D1-Rs) and the others express Dopamine 2 receptors (D2-Rs). Cell-specific knockout mice were generated using Drd1a and Drd2 cre-expressing mice crossed with α4 floxed mice to produce mice with GABAAR α4 deletion specific to D1-R or D2-R containing neurons. These mice were tested in cocaine-conditioned place preference (CPP) to assess behavioural effects of the cell-specific knockouts. In cocaine-CPP, wildtype (WT) and α4 constitutive knockout mice (α4-/-) both showed preference for the cocaine-paired chamber (p < 0.001), potentiated in both genotypes with cocaine challenge (p < 0.001). When α4 deletion was restricted to D1-R-expressing neurons (α4D1-/-), mice showed greater preference for the cocaine-paired chamber (p < 0.001) than WT and mice with α4 deletion specific to D2-R-expressing neurons (α4D2-/-) (p < 0.05). Potentiation of preference with cocaine challenge was absent in α4D2-/- mice, but present in α4D1-/- mice (p < 0.001), revealing distinct roles for α4-mediated tonic inhibition in these two populations in the actions of cocaine. The specificity of α4-/- to NAc neurons was investigated using co-localised immunofluorescent staining of DARPP-32 to label MSNs, cre-recombinase which remains as an artefact of the knockout process, and enkephalin to denote D2-R containing MSNs. Immunohistochemistry and immunofluorescence were performed to characterise the pattern and cell specificity of the α4 knockout in D1-R and D2-R containing neurons in striatal and frontal-cortical regions of the cell-specific knockout mice. α4D1-/- mice originated from two BAC-CRE founder lines (EY266 and EY217) each having slightly different striatal D1-R expression patterns. Mice of the EY217 line shows higher expression in the region of the dorsal striatum and NAc shell, whereas EY266 mice show higher expression in the region of the NAc core, as described in the GENSAT database (http://www.gensat.org). Confirming expression patterns of these knockouts allows the behavioural effects of the manipulations to be directly attributed to specific neuronal circuits. This work was made possible through funding from Medical Research UK (G0802715, G1000008) and the University of Sussex Junior Research Associate scheme.

TB08

MOLECULAR CORRELATES OF INSTRUMENTAL MEMORY PERSISTENCE

Goozée ZY, Dept of Psychology, Univ of Cambridge, Downing St, Cambridge, CB2 3EB zyg21@cam.ac.uk
Everitt BJ(1,2), Merlo E(1,2) (1) Dept of Psychology, Univ of Cambridge, Downing St, Cambridge, CB2 3EB (2) Behavioural and Clinical Neuroscience Inst, Univ of Cambridge, Downing Site, Cambridge, CB2 3EB

The persistence of maladaptive cue-drug memories in abstinent addicts is a major factor in inducing relapse and craving. Instrumental responding for an appetitive reward can be driven by both Pavlovian and instrumental associative memory components. Once an associative memory has been fully consolidated retrieval of the memory may trigger two processes, reconsolidation or extinction, dependent upon the degree of re-exposure. Whereas reconsolidation maintains the original memory, extinction inhibits it. These processes have been seen reliably following Pavlovian conditioning, but their role in instrumental memory paradigms is relatively unexplored. Although both reconsolidation and extinction share common properties, such as NMDA receptor dependency, they also have distinct molecular signatures. Reconsolidation is dependent upon the activation of protein kinases and transcription factors, especially MAPK and Zif268. Conversely extinction is dependent on protein phosphatases, in particular the Ca++-calmodulin dependent phosphatase calcineurin. Following training on a lever press task using a high incentive reinforcer we manipulated the Pavlovian and instrumental memory components of food-seeking behaviour in adult rats by re-exposing animals to 60 minutes of non-reinforced instrumental responding, cue presentation or both. Control animals received a 5min reactivation session. Post reactivation levels of calcineurin and zif268 protein were measured using Western Blotting in a range of candidate brain areas including the prelimbic (PL) and infralimbic (IL) subregions of the medial prefrontal cortex. Data was analysed using one-way ANOVA with Tukey’s test as a post hoc comparisons, unless stated otherwise. Following extinction of the Pavlovian conditioned stimulus, animals reinstated responding in a test session 24hrs later, compared to animals in which both instrumental and Pavlovian components had been extinguished (p=0.05). Calcineurin levels measured following extinction training, showed down-regulation (between 20-40% reduction, dependent on extinction condition) in the IL after all extinction conditions (F(3,20) = 8.761, p<0.05, Eta^2 = 0.568). Following reconsolidation of both Pavlovian and instrumental components calcineurin levels in the PL were decreased (F(2,15) = 3.729, p<0.05, Eta^2 = 0.332), whereas zif268 showed a trend towards being up-regulated (F(2,15) = 3.391, p = 0.061). Taken together these results indicate a dissociation between calcineurin levels within the mPFC with down-regulation of calcineurin in the PL and IL being associated with reconsolidation and extinction of food-seeking memory, respectively. Zif268 appears to be regulated in an opposite manner. These results are consistent with specific roles for calcineurin and zif268, but also with the hypothesised roles of the PL and IL in appetitive memory maintenance and extinction. Supported by the MRC.
DISCRIMINATIVE STIMULUS PROPERTIES OF MITRAGYNE, AN ALKALOID DERIVED FROM LEAVES OF MITRAGYNA SPECIOSA (KRATOM)

Harun N, Centre for Drug Research, Univ Sains Malaysia, Gelugor, Penang, Malaysia, 11800, norsyifa.harun@gmail.com
Hassan Z(1), Navaratnam V(1), Mansor SM(1), Shoaib M(2) (1) Centre for Drug Research, Univ Sains Malaysia, 11800 Gelugor, Penang, Malaysia (2) Inst of Neuroscience, Newcastle Univ, Newcastle Upon Tyne, NE2 4HH UK

Background: Mitragynine is the primary active alkaloid extracted from the leaves of Mitragyna speciosa Korth, a plant that originates in South-East Asia and is commonly known as kratom (or ketum). Kratom has been traditionally used for its opium-like and psychostimulant-like effects to increase work efficiency, reduce pain sensitivity or as a substitute in the self treatment of opiate addiction (Jansen and Prast, 1988, Journal of Ethnopharmacology, 23(1):1115-119; Reanmongkol et.al, 2007 Songklanarin Journal of Science and Technology 29:39-48). It has been widely used as a recreational drug that leads to abuse potential. The present study was performed to investigate the discriminative stimulus effects of mitragynine. This is the first behavioral study investigating the subjective effects of mitragynine in rats. Methods: Male Sprague-Dawley rats were trained to discriminate between mitragynine and vehicle in a two-lever drug discrimination procedure under a tandem variable-interval (VI) 60 s and fixed-ratio (FR) 10 schedules of food reinforcement. The other group of rats was trained to discriminate 5 mg/kg morphine from vehicle. The training sessions were given daily, and once criteria was met as shown by 80% accuracy of lever selection in a block of 10 consecutive sessions, cumulative dose responses, substitution and antagonism tests were conducted. Results: The mitragynine discrimination (15 mg/kg, i.p.) was acquired successfully and yielded a steep dose-response curve which was comparable to the acquisition of morphine discrimination (5 mg/kg, i.p.) in another group of rats. This study is the first to demonstrate that mitragynine can function as a discriminative stimulus in rats. Mitragynine at the dose of 15 mg/kg fully generalized in a dose-dependent manner to morphine discriminative stimulus, suggesting there are pharmacological similarities between the two drugs. The administration of 7-hydroxy-mitragynine (7-HMG) derivative (0.3 - 3 mg/kg, i.p.) produced full generalization at the dose of 3 mg/kg to morphine discriminative stimulus. Hence, the results indicate that 7-HMG derivative is relatively potent compared to mitragynine. In addition, the mitragynine stimulus partially generalized to cocaine (10 mg/kg, i.p.) while these effects were not seen in rats trained to discriminate morphine. Naloxone pretreatment demonstrated a partial attenuation on the mitragynine-lever responding while complete blockade was observed following 7-HMG substituted responses. Conclusions: The present study has demonstrated that the discriminative stimulus effects of mitragynine possess both opioid- and psychostimulant-like effects. The data also suggest the subjective effects of mitragynine may involve other pathways in addition to actions on opioid receptors. Financial sponsorships: This research received financial support from Higher Education Centre of Excellence (HiCoE) special funding (304/CDADAH/650527/K134), International Research Collaboration Fund (1002/CDADAH/910410) and MyBrain15 Scholarship from Ministry of Higher Education.

THE CONSEQUENCES OF METHAMPHETAMINE EXPOSURE DURING PREGNANCY ON MATERNAL PARAMETERS, NEONATAL DEVELOPMENT AND ADULT BEHAVIOUR IN RATS

McDonnell-Dowling K, Discipline of Pharmacology and Therapeutics, National University of Ireland, Galway, Ireland, Distillery Road, Newcastle, Galway, Ireland k.mcdonnellldowling1@nuigalway.ie
Donlon M (1,2), Kelly JP (1,2) (1) Discipline of Pharmacology and Therapeutics, NUI, Galway, Ireland (2) Galway Neuroscience Centre, National Centre for Biomedical Engineering Science, NUI, Galway, Ireland

Methamphetamine (MA) use during pregnancy is becoming an increasing cause for concern. However, quantifying the risk of human MA to the developing offspring poses considerable ethical and experimental challenges. An alternative is to examine the effects of MA exposure in laboratory animals, allowing for greater control of a number of experimental variables. The use of an allometric scale allows us to translate human drug doses into animal doses and so we can investigate MA doses that are commonly abused in pregnant females. Thus, the aim of this study was to determine if in utero MA exposure in rats at pharmacological doses affects neonatal neurodevelopment and behaviour and if it is long lasting in later life. Pregnant Sprague-Dawley dams (n=6-10 dams/group) received MA (0.625, 1.25, 2.5, 5 or 10mg/kg) or control (distilled water) once daily via oral gavage from gestational day 7-21. Maternal body weight, food and water consumption were recorded daily until littering. A range of well-recognised neurodevelopment parameters were examined in the neonatal period including surface righting, negative geotaxis and forelimb grip. Later in life, offspring were tested in two commonly used paradigms of anxiety, namely the elevated plus maze (EPM) and open field test (OF) during the adolescent (PND 28) and adult (PND 56, 85, 113) periods. Data were analysed using either Repeated-Measures ANOVA and Two-way ANOVA or Friedman’s ANOVA and Kruskal-Wallis with relevant post-hoc tests, with the level of significance set at p<0.05. The two higher dose MA groups (5 and 10mg/kg) were associated with a significant reduction in gestational weight gain, and also with maternal death in the immediate pre-littering period (16% and 37.5% of mothers respectively). In the surviving litters of these high dose groups (and to a lesser extent in the 2.5mg/kg group), there were high rates of stillbirths and neonatal death. Impairments in neurodevelopmental parameters were evident with both the 1.25 and 2.5mg/kg groups, which appeared to be dose-related. In the EPM and OF, there were no significant changes in adolescent or adult behaviour between the treatment groups. By using pharmacologically relevant doses, this study demonstrates that MA can have a profound dose-related effect on maternal and neonatal outcome in rats. If extrapolated to the clinical scenario, this will give cause for concern regarding the risks associated with this drug of abuse during the neonatal period. This project was supported by a PhD fellowship awarded by the College of Medicine, NUI, Galway, Ireland.
Enhancing the endocannabinoid signaling confers protection against the neurotoxic effects of cocaine in experimental animals

Moreira FA. Pharmacology, UFMG, Av Antonio Carlos 66277, Belo Horizonte, Brazil, 31270901, fabriciomoreira@icb.ufmg.br
Vilela L, Gobira P, Medeiros D, Ribeiro F, de Oliveira A, Moraes M, Univ Federal de Minas Gerais

Enhancing the endocannabinoid signaling confers protection against the neurotoxic effects of cocaine in experimental animals Fabricio A. Moreira (1*), Luciano R. Vilela (1), Pedro H. Gobira (1) Daniel C. Medeiros (2), Fabiola M. Ribeiro (3), Antonio C. de Oliveira (1), Marcio F. Moraes (2). Departments of Pharmacology (1), Physiology (2) and Biochemistry (3); Institute of Biological Sciences (ICB); Federal University of Minas Gerais (UFMG). *fabriciomoreira@icb.ufmg.br The present study was designed to test the hypothesis that inhibition of fatty acid amide hydrolase (FAAH), the enzyme that terminates the actions of the endocannabinoid anandamide, reduces cocaine-induced seizure and neurotoxicity. Male Swiss mice (n=9/10 per group) received systemic injections of vehicle or an inhibitor of anandamide hydrolysis (FAAH inhibitor, URB597; 0.3-3 mg/kg) followed by cocaine (75 mg/kg; based on Kaminski et al., 2007, Neuropsychopharmacology, 52:895-903; Witkin et al., 2008 J Pharmacol Exp Ther). In an independent experiment, the animals were pre-treated with the CB1 receptor antagonist, AM251 (1 mg/kg), in order to evaluate the underlying mechanisms. Convulsive seizures and electroencephalographic activity were concurrently monitored. Protection against cocaine-induced cell death in the hippocampus was evaluated in ex vivo and in vitro experiments. The statistical analyses (ANOVA followed by Newman-Keuls test) revealed that URB597 (1 mg/kg) increased the latency and reduced the duration of cocaine-induced electroencephalographic and behavioural seizures. These effects were reversed by pre-treatment with AM251. In addition, URB597 prevented the death of hippocampal neurons, which was also reversed by the CB1 receptor blocker. It can be concluded that FAAH-inhibition confers protection against the deleterious effects of cocaine. This occurs through CB1 receptor activation, possibly resulting from an increase in the brain levels anandamide. All the protocols have been approved by the Ethics Committee in Animal Experimentation of the Federal University of Minas Gerais (CEUA-UFMG) under the protocol number 242/2013. Financial support: FAPEMIG (APQ-01038-11)

TB12

SENSITIVITY OF [11C] CARFENTANIL, BUT NOT [3H]DIPRE诺PHINE TO ENDOGENOUS OPIOD PEPTIDE RELEASE (EOPR) AND EXOGENOUS AGONIST ADMINISTRATION – INFLUENCE OF AGONIST INDUCED INTERNALISATION

Quelch DR. Centre for Neuropsychopharmacology, Imperial College London, Burlington Danes Bldg, Hammersmith Hospital, Du Cane Rd, London W120NN, d.quelch09@imperial.ac.uk
Katsouri L(2), Parker CA(3/1), Nutt DJ(1), (1) Centre for Neuropsychopharmacology, Imperial college London, W120NN (2) Centre for Neurodegeneration and Neuroinflammation, Imperial College London, W120NN (3) GlaxoSmithKline - Global Imaging Unit, Stevenage, SG1 2NY

The ability to image EOPR using PET would increase our knowledge of the role of the opioid system in neuropsychiatric disorders. Determination of dose:occupancy relationships of opioid agonists in vivo would also enable a better understanding of drug behaviour in patient populations. However, we are currently limited to being able to measure dopamine release using PET (Laruelle M.;2012;Mol. Imaging in Clin. Neurosci.;71;163-203. Paterson L. et al;2010;JCBFM;1682-1706) and the binding of the commonly used opioid receptor antagonist [11C]diprenorphine is not sensitive to endogenous agonist administration in vivo (Hume S. et al;2007;J. Pharm and Exp. Therapeutics;322;661-667). We compared the sensitivity of both [3H]diprenorphine and [11C]carfentanil, the selective μ receptor agonist radioligand, to amphetamine induced EOPR and exogenous agonist administration. The contribution of agonist-induced internalisation to any changes in binding observed have been explored also. Rats were pre-dosed with either saline, amphetamine (2.0mg/kg;i.p.) or methadone (0.35mg/kg;i.p.) before administration of [3H]diprenorphine (8.24±0.21MBq;i.v.;n=14) or [11C]carfentanil (12.24±1.05MBq;i.v.;n=14). The brains were then removed and various regions assessed for their radioligand uptake. A separate group of animals were also dosed with challenge agent but not radioligand and the tissues assessed in vitro using sub-cellular fractionation with radioligand binding and dual labelling immunofluorescence. Regions with the greatest reductions in [11C]carfentanil binding following either amphetamine (r2=0.18,p=0.0011) or methadone (r2=0.23,p<0.0001) were those associated with the greatest uptake and therefore μ receptor availability in the saline condition. No such relationship was observed with [3H]diprenorphine. Amphetamine pre-treatment also reduced total homogenate [11C]carfentanil (p<0.05), but not [3H]diprenorphine binding. Additionally, a trend (p=0.08) for an increase in microsomal [11C]carfentanil binding was observed in amphetamine and methadone treated animals compared with saline. Methadone and amphetamine pre-treatment did not lead to alterations in cell fraction [3H]diprenorphine binding. A significant increase in μ receptor-Rab5 (an archetypal early endosomal marker) co-localisation was observed following both amphetamine and methadone (both p<0.05) compared with saline in the hypothalamus, a region where the greatest reductions in [11C]carfentanil binding was also observed. No significant alterations in δ or κ receptor co-localisation were observed. Collectively, these data suggest that [11C]carfentanil is more sensitive to EOPR and exogenous agonist administration than [3H]diprenorphine. Increases in sub-cellular fraction [11C]carfentanil binding and early endosomal μ receptor localisation may underpin these differences in sensitivities in vivo. The methodologies developed here warrant application to other PET radioligand targets in order to translate in vivo competition imaging paradigms to other neurotransmitter systems. This work was supported by a BBSRC-GlaxoSmithKline CASE studentship.

The ability to image EOPR using PET would increase our knowledge of the role of the opioid system in neuropsychiatric disorders. Determination of dose:occupancy relationships of opioid agonists in vivo would also enable a better understanding of drug behaviour in patient populations. However, we are currently limited to being able to measure dopamine release using PET (Laruelle M.;2012;Mol. Imaging in Clin. Neurosci.;71;163-203. Paterson L. et al;2010;JCBFM;1682-1706) and the binding of the commonly used opioid receptor antagonist [11C]diprenorphine is not sensitive to endogenous agonist administration in vivo (Hume S. et al;2007;J. Pharm and Exp. Therapeutics;322;661-667). We compared the sensitivity of both [3H]diprenorphine and [11C]carfentanil, the selective μ receptor agonist radioligand, to amphetamine induced EOPR and exogenous agonist administration. The contribution of agonist-induced internalisation to any changes in binding observed have been explored also. Rats were pre-dosed with either saline, amphetamine (2.0mg/kg;i.p.) or methadone (0.35mg/kg;i.p.) before administration of [3H]diprenorphine (8.24±0.21MBq;i.v.;n=14) or [11C]carfentanil (12.24±1.05MBq;i.v.;n=14). The brains were then removed and various regions assessed for their radioligand uptake. A separate group of animals were also dosed with challenge agent but not radioligand and the tissues assessed in vitro using sub-cellular fractionation with radioligand binding and dual labelling immunofluorescence. Regions with the greatest reductions in [11C]carfentanil binding following either amphetamine (r2=0.18,p=0.0011) or methadone (r2=0.23,p<0.0001) were those associated with the greatest uptake and therefore μ receptor availability in the saline condition. No such relationship was observed with [3H]diprenorphine. Amphetamine pre-treatment also reduced total homogenate [11C]carfentanil (p<0.05), but not [3H]diprenorphine binding. Additionally, a trend (p=0.08) for an increase in microsomal [11C]carfentanil binding was observed in amphetamine and methadone treated animals compared with saline. Methadone and amphetamine pre-treatment did not lead to alterations in cell fraction [3H]diprenorphine binding. A significant increase in μ receptor-Rab5 (an archetypal early endosomal marker) co-localisation was observed following both amphetamine and methadone (both p<0.05) compared with saline in the hypothalamus, a region where the greatest reductions in [11C]carfentanil binding was also observed. No significant alterations in δ or κ receptor co-localisation were observed. Collectively, these data suggest that [11C]carfentanil is more sensitive to EOPR and exogenous agonist administration than [3H]diprenorphine. Increases in sub-cellular fraction [11C]carfentanil binding and early endosomal μ receptor localisation may underpin these differences in sensitivities in vivo. The methodologies developed here warrant application to other PET radioligand targets in order to translate in vivo competition imaging paradigms to other neurotransmitter systems. This work was supported by a BBSRC-GlaxoSmithKline CASE studentship.
TC01
ANTERIOR CINGULOTOMY FOR MAJOR DEPRESSION DOES NOT IMPAIR STROOP PERFORMANCE BUT DEPRESSION SEVERITY DOES
Tolomeo ST, Div of Neuroscience, Univ of Dundee, Medical Research Inst, Mail Box 6, Level 6 Ninewells Hospital and Medical School, Dundee DD1 9SY, s.tolomeo@dundee.ac.uk
Matthews K(1), Steele JD(1) (1) Div of Neuroscience, Medical Research Inst, Univ of Dundee, Dundee, UK

Introduction: Neuropsychological impairment using Stroop task has been extensively demonstrated in depression (Epp et al. 2012, Clinical psychology review, 32, 316-328). Extensive anterior cingulate damage in non-depressed humans is associated with impairments on the Stroop task (Ochsner et al. 2001, Neuropsychologia, 39, 219-230). Anterior cingulotomy (ACING) is a potentially effective treatment for treatment-resistant depression (TRD) and involves the creation of bilateral lesions (Steele et al. 2008, Biological psychiatry, 63, 670-677). It is not known whether patients who receive this treatment have impairments on the Stroop. We tested the hypothesis that mood and ACING were independent predictors of deficits (increased errors and slower responses) on the Stroop. Methods: Brain structural and neuropsychological functioning were investigate with 15 patients with a diagnosis of TRD received ACING, 20 similar TRD patients who had not received ACING (‘non-ACING’), and 20 healthy controls, all matched for age, IQ and gender. Results: Both ACING and non-ACING groups showed performance deficits compared to controls on the emotional and classical Stroop task. However the ACING group did not perform significantly worse than the non-ACING group. The number of correct responses and errors were highly correlated with clinical ratings of depression severity in both patient groups. Patients who had received ACING and made a very good recovery from TRD performed similarly to controls. The Stroop reaction time effect, which involves slowing on incongruent trials, correlated with white matter reductions in the anterior cingulate cortex. Increased reaction times strongly correlated with white matter reductions in the amygdala/hippocampal complex, a region implicated in TRD but unaffected by the operation. Conclusions: This study supports the interpretation that ACING does not impair Stroop performance however TRD severity does. This may be because the Dundee ACING procedure involves very small lesions compared to lesion descriptions in the literature associated with Stroop impairment. No financial sponsorship.

TC02
INDIRECT EVIDENCE OF PREFRONTAL GLIAL INVOLVEMENT IN GLUTAMATE-BASED MECHANISMS OF MOOD REGULATION IN DEPRESSION
Arnone D, Centre For Affective Disorders, Inst of Psychiatry, Section of Biology of Mood Disorders, Dept of Psychological Medicine, King’s College London, P074, 103 Denmark Hill, London, SE5 8AF, danilo.arnone@kcl.ac.uk
Mumuni A(1), Jauhar S(2), Condon B(3), Cavanagh J(4) (1) School of Medical and Health Sci, Univ for Development Human Biology, Tamale Campus, P. O. Box TL 1350, Tamale, Ghana, (2) Dept of Psychosis Studies, King’s College London, Inst of Psychiatry, London, UK, (3) MRI Unit, Inst of Neurological Sciences, Univ of Glasgow, Glasgow, UK, (4) Inst of Health and Wellbeing, Univ of Glasgow, Glasgow, UK

Introduction: The glutamate hypothesis of depression represents an alternative to the traditional view that places monoaminergic dysfunction as central to the pathogenesis of mood disorders. Magnetic resonance spectroscopy (MRS) measures glutamatergic metabolites namely glutamate and glutamine located in neurons and astrocytes respectively. In this meta-analysis we identified studies investigating prefrontal cortex glutamatergic neurotransmission in depression with MRS with the aim of investigating the contribution of glutamate and glutamine to depression. Methods: A comprehensive literature search up to 2014, identified several thousands relevant studies. Nine studies investigated absolute values of glutamine and glutamate in the prefrontal cortex as a composite measure in depression vs. healthy controls. Seven reports investigated changes in glutamate levels only vs. healthy individuals. Results: The analyses showed a significant reduction in absolute composite measure values in the prefrontal cortex in depression with an effect size (SMD) of -0.56 (CI=-0.96, -0.16) correlating in meta-regression analyses with treatment severity (p = 0.04). Glutamate measurements in isolation did not differ vs. healthy controls (SMD= -0.17; CI: -0.76, 0.42). Conclusions: The analysis supports a role for glutamatergic dysfunction in the pathogenesis of mood dysregulation. The reduction in the absolute composite values of glutamatergic synaptic function with absence of changes in glutamate levels, suggests a possible modulatory role of astrocytes in the pathophysiology of depression. Dr Arnone is an NIHR Academic Clinical Lecturer and his research is supported by the Academy of Medical Sciences.
TC03

COMPUTATIONAL META-ANALYSIS OF STATISTICAL PARAMETRIC MAPS IN MAJOR DEPRESSION

Arnone D. Centre For Affective Disorders, Inst of Psychiatry, King’s College London P074, 103 Denmark Hill London, SE5 8AF, danilo.arnone@kcl.ac.uk

Job D(1), Selvaraj S(2), Abe O(3), Amico F(4), Cheng YQ(5), Collobby SJ(6), O’Brien JT(6), Frodl T(4), Gotlib IH(7), Ham BJ(8), Kim MJ(9), Perico C A-M(10), Salvadore G(11), Thomas AJ(6), Van Tol MJ(11), Wagner G(12), McIntosh AM(1) (1) Div of Psychiatry, The Univ of Edinburgh, Edinburgh, UK (2) The Univ of Texas, Huston, USA (3) Dept of Radiology, Nihon Univ School of Medicine, Itabashi-ku, Tokyo, Japan (4) Dept of Psychiatry, School of Medicine, Trinity College, Dublin, Ireland (5) Dept of Psychiatry, The 1st Affiliated Hospital of Kunming Medical Univ, Kunming, PRC (6) Inst for Aging and Health, Newcastle Univ, Newcastle upon Tyne, UK (7) Dept of Psychology, Stanford Univ, Stanford, USA (8) Dept of Psychiatry, College of Medicine, Korea Univ, Seoul, Republic of Korea (9) Dept of Psychological & Brain Sciences, Dartmouth College, Hanover, USA (10) Disciplinas de Psiquiatria e Psicologia Médica da Faculdade de Medicina do ABC Coordenadora da Enfermaria de Psiquiatria do Hospital Estadual Mário Covas, San Paolo, Brazil (11) Neuroscience Experimental Medicine, Johnson & Johnson, USA (12) Univ Medical Center Groningen, Groningen, The Netherlands (13) Dept of Psychiatry and Psychotherapy, Univ of Jena, Jena, Germany

Background: Several neuroimaging meta-analyses have summarized structural brain changes in major depression (MDD) using coordinate-based methods. These techniques are valid and do not require data from individual participants, but their findings might be biased towards brain regions where significant differences were found in the original studies. Here we implement a novel meta-analysis technique that includes all of the between-group imaging data from each study and apply it to the study of major depression. Methods: We conducted a systematic review and meta-analysis of studies using voxel-based morphometry (VBM) comparing participants with major depression vs. healthy controls. Authors of eligible studies were contacted to obtain statistical parametric maps. Summary effect sizes were computed using a random-effects model with correction for multiple comparisons at voxel level threshold set at p-corrected=0.001 (Z=2.96). Publication bias and heterogeneity were also estimated. Results: Data were obtained from ten studies including 397 patients (53.4% medicated) and 591 controls. Mean age of depressed participants was 40.2 (SD=13.02). Major depression was characterized by reduction in grey matter (Z=4.64) in several brain regions with maximum peak significance in the right inferior temporal gyrus (BA 20; MNI coordinates: 64, -26, -20) and no evidence of publication bias (t=0.94, df=8, p=0.37). Several additional foci of grey matter loss were also found, including in the prefrontal, parahippocampal, and fusiform gyri. Conclusions: The novel computational meta-analytic approach used in this study identified grey matter loss in key brain regions implicated in emotion generation and regulation. These results are not biased towards the results of the original studies because they include all available imaging data and not only those regions that were statistically significant. This technique might increase sensitivity to detect additional areas of grey matter loss. Dr Arnone is an NIHR Academic Clinical Lecturer and his research is supported by the Academy of Medical Sciences.

TC04

DYNAMIC DIFFERENCES IN AGE-RELATED CHANGES IN BRAIN STRUCTURE IN THE THALAMUS AND PREGENUAL ANTERIOR CINGULATE IN ADOLESCENTS WITH MAJOR DEPRESSIVE DISORDER

Hagan CC. Psychiatry/Psychology, Univ of Cambridge/Columbia Univ, Herchel Smith Bldg, Forvie Site, Robinson Way Cambridge, CB2 0SZ, cindy.hagan@gmail.com

Graham JME(1), Tait R(1,2), Widmer B(1), van Nieuwenhuizen AO(1), Ooi C(1), Whitaker K(1), Simas T(1), Bullmore ET(1), Lennox BR(1,3), Sahakian BJ(1,2), Goodyer IM(1), Suckling J(1,2) 1. Univ of Cambridge, Dept of Psychiatry, Cambridge, UK 2. Univ of Cambridge, Behavioural and Clinical Neurosciences Inst, Cambridge, UK 3. Univ of Oxford, Dept of Psychiatry, Medical Sciences Division, Oxford, UK

Introduction: There is little understanding of the neural systems underlying adolescent depressions. In a cross-sectional study we compare unipolar depressed adolescents with healthy adolescents to assess group differences and determine the relative effects of age on grey matter volume (GMV). Method: Structural neuroimaging was performed on 109 adolescents with depression and 36 healthy adolescents, matched for age, gender, and handedness. GMV differences were examined across the whole-brain and within the anterior cingulate cortex (ACC). Correlations with severity of self-reported depression was also examined in significant regions. Results: Whole-brain voxel based morphometry revealed no significant group differences but a significant group x age interaction; GMV in the thalamus decreased across age in adolescent patients, but increased across age in controls. At the whole-brain level and in the ACC, both groups showed an overall reduction in GMV across age, however, more robustly in controls. A significant group x age interaction also was observed in the ACC. GMV in the ACC remained relatively constant across age in patients, yet decreased across age in healthy adolescents. In patients, GMV in the thalamus, but not the ACC, was inversely related with severity of depression. Conclusions: In the thalamus, the different developmental pattern of GMV across age for depressed relative to healthy adolescents may indicate that GMV differences in the thalamus may precede MDD or arise in an age-related manner because of MDD. Longitudinal replication is needed. The interaction in the ACC may indicate aberrant development of this region as a consequence of depressions. Funding: The Improving Mood with Psychoanalytic and Cognitive Therapies (IMPACT) clinical trial was funded by the Health Technology Assessment Branch of the National Institute of Health Research (06/05/01). Magnetic Resonance-IMPACT (MR-IMPACT) was funded by the Medial Research Council (grant: G0802226) and the Behavioural and Clinical Neuroscience Institute (BCNI) at the University of Cambridge. The BCNI is jointly funded by the Medical Research Council and the Wellcome Trust. Additional support was received from the National Institute for Health Research (NIHR) Cambridge Biomedical Research Centre. CCH is supported by a Parke Davis Fellowship from the University of Cambridge and resides at Columbia University.
VOXEL-BASED META-ANALYTICAL COMPARISON OF WHITE MATTER ALTERATIONS IN MAJOR DEPRESSION AND BIPOLAR DISORDER

**Wise T**, Centre for Affective Disorders, Inst of Psychiatry, King’s College London, 103 Denmark Hill London SE58AF, toby.wise@kcl.ac.uk
Radua J(1,2), Herane A(3), Cleare AJ (3), Young AH(3), Arnone D(3) (1)Dept of Psychosis Studies, Inst of Psychiatry, King’s College London, London, SES 8AF (2)Research Unit, FIDMAG Germanes Hospitalàries – CIBERSAM, Barcelona, Spain (3)Centre for Affective Disorders, Inst of Psychiatry, King’s College London, London, SES 8AF

Introduction White matter abnormalities have been detected in both major depressive disorder (MDD) and bipolar disorder (BD) by a number of studies using diffusion tensor imaging (DTI). However there is substantial heterogeneity in findings and it is unclear whether the two disorders are associated with common or different white matter microstructural changes. Methods A literature search of Pubmed, Embase & Scopus was conducted for whole brain DTI studies published up to January 2014 that compared fractional anisotropy (FA) in MDD or BD vs. controls. The results of these studies were analysed using Anisotropic Effect Size Signed Differential Mapping (AES-SDM) using a Tract-Based Spatial Statistics (TBSS) template. We conducted a comparison of effect sizes in BD and MDD studies to identify differences in FA between the two disorders. Results Thirty-two studies were included in the meta-analysis, which used either TBSS or voxel-based methods. MDD was associated with reduced FA in a number of areas, most prominently in the genu of the corpus callosum (z = -2.03, p < .001), right cerebellum (z = -1.50, p < .001) and left superior longitudinal fasciculus (SLF, z = -1.30, p < .001). BD was characterised by reduced FA in the left cingulum (z = -2.73, p < .001) and genu of the corpus callosum (z = -2.07, p < .001), and increased FA in the right SLF (z = 1.03, p < .001). Meta regression in the BD studies showed that this reduction was larger in studies using younger patients (z = 4.59, p < .001). Studies using TBSS methods also found larger differences between BD patients and controls in this region than those using VBA (z = 2.35, p < .001). Comparison of effect sizes revealed significantly lower FA in the left SLF in BD compared with MD (z = 2.83, p < .001), and reduced FA in the right cerebellum in MDD compared with BD (z = -1.02, p < .001). Conclusions Both MDD and BD show significant differences in white matter microstructure compared with healthy controls which may contribute to the symptoms seen in these disorders. Results from BD studies are heterogeneous, but some of this variance can be explained by differences in sample characteristics and methods. While there is some overlap between the conditions, the areas implicated are largely distinct indicating that MDD and BD may be differentiated by specific patterns of underlying brain changes. TW is supported by a PhD studentship from the National Institute for Health Research.

USING MAGNETOENCEPHALOGRAPHY (MEG) TO INVESTIGATE THE EFFECT OF AN SSRI ON EARLY VISUAL CORTICAL RESPONSES TO THREAT

**Murphy SE**, Dept of Psychiatry, Univ of Oxford, Oxford Centre for Human Brain Activity, Warneford Hospital, Oxford, OX3 7EQ, susannah.murphy@psych.ox.ac.uk
Nagels G(1), Woolrich MW(1), Kringelbach ML(2), Acton C(3), Cowen PJ(2) & Harmer CJ(2) (1)Oxford Centre for Human Brain Activity, Univ of Oxford, Oxford, UK (2)Dept of Psychiatry, Univ of Oxford, Oxford, UK (3)Faculty of Medicine, Univ of Toronto, Canada

Neuropsychological studies suggest that a key mechanism by which antidepressants exert their effects on mood is through a reduction of negative cognitive biases. For example, healthy volunteer studies have demonstrated that subchronic (7 day) administration of a Selective Serotonin Reuptake Inhibitor (SSRI) induces a bias in selective attention away from threat-related stimuli (Murphy et al 2009, Int J Neuropsychopharmacol. 12(2):169-79). fMRI studies have demonstrated that antidepressants reduce activity in the amygdala in response to threat-related facial expressions (Harmer et al 2006, Biol Psychiatry, 59(9):816-20). Together, these findings have been used to argue that an important mechanism through which antidepressants may exert their effect on mood is by modifying rapid, automatic emotional processing. Such findings are striking, given the central role played by cognitive models on early, automatic biases to threat in the cause and maintenance of anxiety disorders (MacLeod et al 2002, J Abnorm Psychol 111:107-123). However, the behavioural and fMRI measures used have been limited in the extent to which they are able to elucidate the stage(s) of neural processing at which antidepressants exert their effects on the processing of emotional faces. The current study used magnetoencephalography (MEG) to more precisely examine the effect of an SSRI on the early processing of fearful faces. At a functional level, a better understanding of the timing of antidepressant modulation of emotional processing will help further illuminate the neuropsychology of drug action. 28 healthy volunteers were randomized to receive 7 days treatment with an SSRI (citalopram) or placebo. On day seven of drug administration, the participants were given an MEG scan during which they passively viewed fearful, happy and neutral face stimuli. The response to fearful compared to happy faces was analysed for the time period of 80-180ms post-stimulus onset. There was an effect of face emotion on activity in medial primary visual areas from 80ms, in the precuneus at around 115ms and in more lateral occipito-temporal regions, including the fusiform cortex, from 130-155ms. Citalopram modulated activity in the occipito-temporal region at around 130ms. This is initial evidence to support the notion that citalopram has an impact on early visual processing of threat stimuli. It is consistent with behavioural and fMRI data that demonstrates a reduction in threat processing after 7 days administration of citalopram in healthy volunteers. This study is a demonstration of the use of MEG as a direct measure of neural activity, which not only gives very high temporal resolution, but also circumvents the problems associated with interpreting pharmacological fMRI data. This work was supported by a Wellcome Trust studentship to SEM.
THE SPATIOTEMPORAL OSCILLATORY EFFECTS OF SUBANAESTHETIC KETAMINE INFUSION IN MAN: A PHARMACO-MEG STUDY

Muthukumaraswamy SD. School of Psychology, Cardiff Univ, CUBRIC Bldg, Park Place Cardiff, CF103AT, sdmuthu@cardiff.ac.uk
Shaw A (1), Jackson L (2), Hall J (2), Saxena N(2) (1) Cardiff Univ Brain Research Imaging Centre, Cardiff, CF10 3AT; (2) Dept of Anaesthetics, Cardiff Univ, Cardiff CF14 4XN

There has been a recent resurgence in interest in the N-methyl-D-aspartate (NMDA) antagonist ketamine, following discovery of its rapid antidepressant properties. While detailed animal models of the molecular mechanisms underlying ketamine’s effects have emerged, there are few neurophysiological studies examining the subanaesthetic effects of ketamine infusion in man. To examine the neurophysiological action of ketamine in the human CNS, we used pharmacological magnetoencephalography (pharmaco-MEG). Pharmaco-MEG directly records neocortical activity at high temporal and spatial resolution and is not affected by potential blood-flow cofounds. Whole-head MEG was recorded using the CUBRIC 275-channel axial gradiometer system, along with ECG, EOG and EMG in two experiments. Experiment one included 19 male volunteers and experiment two a further five male volunteers. In experiment one, we recorded a five minute resting baseline period and participants then received a bolus of 0.25mg / kg ketamine followed by maintenance infusion (6.25 ug/kg/min). A further ten minutes of resting data were recorded followed by a set of basic tasks. In experiment two, the same infusion protocol was used, with the infusion lasting twenty minutes. No tasks were performed in experiment two and eighty minutes of resting MEG data were recorded in order to track the temporal profile of ketamine effects. As expected, subanaesthetic ketamine doses caused increased heart rate, blood pressure and decreases in saccadic eye movement velocity accompanied by strong subjective effects. MEG power spectra revealed a rich set of significant oscillatory changes compared to placebo sessions. This included a) decreases in delta power (1-4 Hz) in parietal, occipital and temporal cortices b) increases in medial frontal theta power (4-8 Hz) but occipital decreases c) decreases in occipital, parietal and anterior cingulate alpha power (8-13 Hz) d) decreases in occipital and temporal beta power(13-30 Hz) e) increases in frontal and temporal low gamma power (30-50 Hz) and f) increases in parietal and cingulate cortex high gamma power (50-100 Hz). In Experiment 2, spatiotemporal pharmacodynamic effects were mapped and the various changes in resting-state functional connectivity profiled. The pattern of oscillatory effects we observed with ketamine, were distinctly different to those observed with the serotonergic hallucinogen psilocybin (Muthukumaraswamy et al., 2013 J Neuroscience 33 , 15171-15183). The rich set of effects observed could potentially serve as biomarkers of the rapid antidepressant effects of ketamine and future similar studies in clinical patients are warranted. Funded by a Cardiff University (Neuroscience and Mental Health Research Institute) grant

FRONTO-SUBCORTICAL CIRCUITS AND AVOIDANCE BEHAVIOUR: DIFFERENTIAL CONTRIBUTIONS OF THE ORBITOFRONTAL AND VENTROLATERAL PFC

Clarke HF. Dept of Physiology, Development and Neurobiology, Behavioural and Clinical Neurosciences Inst, Univ of Cambridge, Downing St, Cambridge CB2 3DY hfe23@cam.ac.uk
Horst N(2,3), Roberts AC(1,3) 1. Dept of Physiology, Development and Neurobiology, Univ of Cambridge 2. Dept of Psychology, Univ of Cambridge 3. Behavioural and Clinical Neurosciences Inst, Univ of Cambridge

Elevated fear and anxiety are key symptoms of affective neuropsychiatric disorders, and are associated with dysfunction in fronto-subcortical circuits that include the amygdala and hippocampus. Interestingly despite extensive segregation of executive behaviours at the level of the prefrontal cortex, the differential role of the ventrolateral prefrontal (vIPFC; Brodmann’s area 45/12) and orbitofrontal (OFC; Brodmann’s area 11) cortices in anxiety behaviours is uncertain. Indeed lesions of both areas in the marmoset result in increased anxiety and conditioned fear (Agustín-Pavón C et al., 2012, Biological Psychiatry, 72(4):266-72), and both areas are activated in studies of anxiety in humans (Campbel-Sils et al., 2011, Neuroimage, 54, 689-696). However, it is not known if these areas also have a role in modulating the impact of anxiety on choice behaviour. The present study therefore investigates the role of the vIPFC and the OFC in the control of instrumental responding by unconditioned mildly aversive stimuli. Marmosets (5 males, 4 females; 2 years old at start of study) were trained to respond to 2 identical stimuli presented on either side of a touch sensitive computer screen that were on a variable interval reward (5 sec banana milkshake) schedule, occasionally overlaid with variable punishment (0.3 sec 117dB loud noise) on one side only. They were then implanted with intracerebral cannulae targeting either the vIPFC or OFC, amygdala and ventral hippocampus and the effects of temporary inactivation of these regions on punishment induced avoidance was assessed with infusions of 0.1mM muscimol/1.0mMbaclofen (0.5µl infused at 0.25µl/min). Marmosets were used for this study because they have an evolutionarily advanced prefrontal cortex, that is far more similar to humans than that of rodents, and the presence of a vIPFC in rodents is uncertain. Compared to saline infusions, vIPFC inactivation resulted in animals biasing their responding away from the punished side on the day of infusion only (Repeated measures anova on number of responses to punished vs unpunished side, 3 way interaction, Reward/Punish x day x group, F1,6 = 22.02, P = 0.003; Punish x day x group, F1,6 = 24.29, P = 0.003, punish day 1 vs day 2, t3 = 3.264, P = 0.047).This effect was blocked by valium (0.25mg/kg 30min pretreat, t3 = 10.253, P = 0.002) suggesting an anxiety component to the anti-punishment bias. In contrast OFC inactivation had no effect on the day of infusion but resulted in a profound bias away from the punished side the next day (when neither inactivation or punishment occurred; punish day 1 vs day 2, t3 = -3.996, P = 0.028). This effect was blocked by both valium (on day 1, t3 = 10.404, P = 0.028; on day 2, t3 = 10.044, P = 0.002) and inactivation of the amygdala, ventral hippocampus, or a disconnection of the two on day 2 (amygdala, t2 = 10.185, P = 0.01; hippocampus, t2 = 11.808, P = 0.007; disconnection, t2 = 19.179, P = 0.009). The vIPFC and the OFC have dissociable roles in the regulation of responding to unconditioned punishment. We hypothesise that the vIPFC is important for reconciling conflict between punishment and reward in the context of response selection and its absence allows punishment to dominate. In contrast the inactivation of the OFC has no effect on day 1 on response selection, but results in an enhanced punishment memory in an amygdala/ventral hippocampal circuit. This extends previous findings implicating the OFC in the regulation of the amygdala in aversive situations, to suggest that the OFC directly modulates amygdala plasticity. This study was funded by a MRC Programme Grant (ACR) and an MRC Career Development Award (HFC).
TC09

RAPID ANTIDEPRESSANT EFFECTS OF LANICEMINE (AZD6765) MAY BE RELATED TO EFFECTS ON REGIONS OF THE DEFAULT MODE AND SALIENCE NETWORKS

Dutta A, Neuroscience and Psychiatry Unit, Univ of Manchester, G.714, Stopford Bldg, Manchester, M13 9PT, arpan.dutta@postgrad.manchester.ac.uk
McKie S(1), Downey D(1), Dourish CT(2), Dawson GR(2), Deakin JFW(1) (1) Neuroscience and Psychiatry Unit, Univ of Manchester, Stopford Bldg, Manchester, M13 9PT (2) P1Vital, Manor House, Howbery Park, Wallingford, Oxfordshire, OX10 8BA

Introduction: Major Depressive Disorder is a chronic mental illness. There is a need to find new rapid acting antidepressants to improve treatment efficacy. Ketamine is a N-methyl D-aspartate receptor antagonist and lanicemine (AZD6765) is a low trapping NMDA channel blocker. Both have demonstrated rapid antidepressant activity in patients. Ketamine challenge phMRI has implicated the anterior cingulate cortex (BA32/25) in the antidepressant response. The objectives were to explore the changes in resting fMRI BOLD produced by intravenous infusion of lanicemine and ketamine compared to placebo during infusion and one day after (ClinicalTrials.gov Identifier: NCT01046630) Methods: 54 treatment naïve males and females with current major depressive disorder (MDD) were scanned on Philips (Manchester) and Siemens (Oxford) 3T MRI scanners while being infused with either placebo (0.5% saline), 0.5mg/kg ketamine or 100mg lanicemine over 1 hour. Rgesting state data between drug treatments was compared for the final 25 minutes of the drug infusion scan and for a 25 minute resting state scan a day later. Images were pre-processed using SPM8. Independent Component Analysis was performed using the Group ICA for fMRI (GIFT) toolbox and the resting component with the highest spatial correlation to the ACC was used. Region of Interest analysis was performed using MarsBaR (Marseille Boite a Regions d’intérêt) for 19 seed regions within the main effect of the resting state component. Results: Day 1: Lanicemine significantly increased mean amplitude of low frequency fluctuations (ALFF ) in the right insula (AZ 0.629 [Standard Error (SE) +/- 0.130], Ket 0.282 [SE +/- 0.137], Plac 0.277 [SE +/- 0.133]), right inferior parietal lobule (AZ 0.714 [SE +/- 0.155], Ket 0.211 [SE +/- 0.164], Plac 0.300 [SE +/- 0.159]) and left cingulate gyrus (AZ 0.280 [SE +/- 0.063], Ket 0.120 [SE +/- 0.066], Plac 0.178 [SE +/- 0.064]) Greater than ketamine or placebo. Ketamine increased mean ALFF greater than placebo in the right lentiform nucleus (AZ 0.431 [SE +/- 0.132], Ket 0.757 [SE +/- 0.140], Plac 0.704 [SE +/- 0.136]) and left medial frontal gyrus (AZ 1.566 [SE +/- 0.118], Ket 1.863 [SE +/- 0.125], Plac 1.704 [SE +/- 0.121]). There was significantly decreased mean ALFF in the left insula (AZ 0.409 [SE +/- 0.126], Ket 0.474 [SE +/- 0.133], Plac 0.723 [SE +/- 0.129]) in the lanicemine group compared to placebo (p<0.05 uncorrected). Day 2: Lanicemine increased mean ALFF greater than ketamine and placebo in the left lentiform nuclei (AZ 1.005 [SE +/- 0.114], Ket 0.726 [SE +/- 0.120], Plac 0.535 [SE +/- 0.117]) and right lentiform nuclei (AZ 1.239 [SE +/- 0.135], Ket 0.857 [SE +/- 0.142], Plac 0.688 [SE +/- 0.138]). Lanicemine reduced mean ALFF in the left middle frontal gyrus (AZ 0.167 [SE +/- 0.102], Ket 0.420 [SE +/- 0.108], Plac 0.350 [SE +/- 0.105]) and right middle frontal gyrus (AZ 0.171 [SE +/- 0.092], Ket 0.372 [SE +/- 0.097], Plac 0.517 [SE +/- 0.094]) (p<0.05 uncorrected). Conclusion: The antidepressant effects of lanicemine demonstrated significant differences from those of ketamine 24 hours after infusion. Affecting regions included insula, inferior parietal lobule, middle frontal gyrus, cingulate gyrus and lentiform nuclei, all of which are implicated in MDD suggesting antidepressant effects. The rapid antidepressant effects of lanicemine are possibly due to resetting of the interface between default mode and salience networks.

TC10

REDUCED DEFAULT MODE ACTIVITY IN THE BILateral PRECUNeUS IN DEPRESSION IS REVERSED BY ACUTE INTRAVENOUS CITALOPRAM INFUSION

Dutta A, Neuroscience and Psychiatry Unit, Univ of Manchester, G.714, Stopford Bldg, Manchester, M13 9PT, arpan.dutta@postgrad.manchester.ac.uk
McKie S(1), Deakin JFW(1) (1) Neuroscience and Psychiatry Unit, Univ of Manchester, Stopford Bldg, Manchester, M13 9PT

Introduction: Serotonin is implicated in the pathophysiology of Major Depressive Disorder (MDD). Until recently it has been difficult to directly measure effects of serotonin challenge. Citalopram is an effective SSRI antidepressant widely utilised in MDD. Whilst the effects of chronic citalopram have been well studied less is known about the acute neural effects in MDD and healthy controls. The objective was to determine the effects on fMRI BOLD produced by acute intravenous infusion of citalopram compared to placebo in MDD and healthy controls. Methods: 63 unmedicated males and females with current major depressive disorder were scanned on a Philips 1.5T MRI scanner while being infused with either placebo (0.5% saline) or citalopram 7.5mg. Rgesting state data was compared for the final 12 ½ minutes following drug infusion. Images were pre-processed using SPM8. Independent Component Analysis was performed using the Group ICA for fMRI (GIFT) toolbox and the resting component with the highest spatial correlation to the ACC was used. Region of Interest analysis was performed using MarsBaR (Marseille Boite a Regions d’intérêt) for seed regions within the main effect of the resting state component. Results: After saline infusion depressed individuals showed reduced default mode activity in precuneus. Citalopram infusion had no effect in controls but normalised default mode activity in the depressives producing a significant drug x group interaction. Conclusion: The acute antidepressant effects of citalopram are modulated by changes in the bilateral precuneus. The precuneus is central to connectivity with other regions in MDD. Given its prominent role in the default mode network and its links to rumination this is an important finding. Sponsorship: NewMood European Union Integrated Programme, Medical Research Council UK, NIHR Manchester Biomedical Research Centre
**TC11**

**FUNCTIONAL DISCONNECTION OF ANTERIOR TEMPORAL AND SUBGENUAL CORTICES PREDICTS RECURRENCE OF DEPRESSION**

Lythe KE, Inst of Brain, Behaviour and Mental Health, Univ of Manchester, T19 Zochonis Bldg Brunswick St, M13 9PL, karen.lythe@manchester.ac.uk

Moll J (1), Gethin JA (2), Workman CI (2), Green S (2), Deakin JFW (2), Elliott R (2), Zahn R (2,3) (1) Cognitive and Behavioral Neuroscience Unit, D’Or Inst for Research and Education, Rio de Janeiro, Brazil (2) Inst of Brain, Behaviour and Mental Health, Univ of Manchester, Manchester, M13 9PL (3) Inst of Psychiatry at King’s College London, London, SE5 8AF

Individuals with major depressive disorder (MDD) show overgeneralization of self-blaming emotions (e.g. guilt) relative to those associated with blaming others (e.g. indignation). This ‘self-blaming bias’ remains upon remission and may play a role in vulnerability. We have previously shown a functional disconnection between anterior temporal (ATL) and subgenual cortices (SC) whilst people with remitted MDD experience self-blaming emotions compared to control participants. It remained elusive, however, whether this fMRI decoupling could be used as a biomarker of MDD vulnerability. To validate our potential biomarker, we prospectively investigated whether functional decoupling between the ATL and SC predicts subsequent recurrence in individuals with MDD. We hypothesized that individuals with a recurrent major depressive episode (MDE) in 14 months following an initial fMRI scan exhibit lower ATL-SC coupling compared to those remaining stable. We report an interim analysis on the first 42 participants with remitted MDD from a larger ongoing study. Participants in the MDD group fulfilled criteria for a past MDE and MDD according to DSM-IV-TR, with remission of symptoms for at least 6 months. Exclusion criteria were other current or relevant past axis-I disorders. T2*-weighted images were acquired on a 3T MRI scanner. Participants were presented with statements describing actions counter to socio-moral values described by social concepts (e.g. stingy) for which either they (self-agency, n=90) or their best friend (other-agency, n=90) were the agents. Images were pre-processed and analysed using SPM8 and psychophysiological interaction (PPI) analysis to measure functional coupling between a right ATL seed region and the SC for trials rated as highly unpleasant within self- and other-agency conditions. Over the follow-up period, 20 participants developed a recurrent MDE, while 22 remained in remission. We confirmed our hypothesis, that those participants with a recurrent MDE showed lower ATL-SC coupling when comparing self-blaming emotions to fixation (p=0.001 uncorrected, t=3.26, FWE-corrected p=.05 over a priori subgenual ROI). The same ATL-SC decoupling effect in the recurrent MDE group occurred for the more specific contrast of self-blaming versus other-blaming emotions (p=0.007 uncorrected, t=2.55). However, the effect size was not sufficient to survive correction for multiple comparisons (FWE-corrected p=.17). We were able to show that fMRI ATL-SC decoupling during the experience of self-blaming emotions is a biomarker of recurrence risk in MDD. These findings await confirmation from the full sample on completion of the follow-up phase of the study. This study was funded by an MRC Clinical Scientist Fellowship awarded to Roland Zahn.

**TC12**

**EMOTIONAL AND WORKING MEMORY IN TREATMENT RESISTANT DEPRESSION: AN FMRI STUDY**

Symonds CS, Neuroscience & Psychiatry Unit, Inst Brain Behaviour & Mental Health, Univ of Manchester, 3304 Jean MacFarlane Bldg, Oxford Rd, Manchester, M13 9BL catherine.symonds@manchester.ac.uk

McKie S (1), Elliott R (1), McAllister-Williams, RH (2), Ferrier IN (2), Deakin JFW (1), Anderson IM (1) (1) NPU, Univ. of Manchester & Manchester Academic Health Sciences Centre, Manchester, UK. (2) Academic Psychiatry, Wolfson Research Centre, Campus for Ageing & Vitality, Newcastle upon Tyne, UK

Background: Neurocognitive deficits and mood-congruent biases have been reported in depression, although there are inconsistencies possibly relating to the population studied (1). A previous meta-analysis by these authors showed differential effects on emotionally valenced material following raised cortisol. We investigated working and episodic memory, including the encoding and retrieval of emotional memories in patients with treatment resistant depression (TRD) as this population may be more homogeneous and likely to display neurocognitive deficits than an undifferentiated depressed group. Methods: We compared the behavioural and fMRI BOLD signal response of 30 healthy volunteers and 27 medicated TRD patients using the working memory n-back task and an emotional encoding and retrieval task based on positive and neutral pictures. Results: There was no difference in behavioural performance on the memory tasks. During the n-back task the TRD patients showed a reduced activation of the dorsolateral prefrontal cortex compared to controls. In the emotional memory task, the TRD group had less activation of the posterior cingulate cortex whilst encoding positive and neutral images, and reduced anterior cingulate cortex activation whilst retrieving positive images compared to neutral. Whilst retrieving images irrespective of valence, the TRD group demonstrated an increased activation of the posterior insula compared with controls. Conclusions: This study also suggests there is an alteration in the functioning of the cingulate and insular cortex in the encoding and retrieval of positive emotional memories in this group of patients with TRD. Further study is needed to determine whether there is alteration of negative emotional memory processing and what relationship this has to the degree of depression or a failure to respond to treatment. (1) Chamberlain, S., Sahakian, B. (2006). Curr Psychiatry Rep 8(6): 458-463. (2) Symonds, CS et al (2014 - in preparation) Funding: This work was supported by a clinical fellowship from NIHR Manchester Biomedical Research Centre and a grant from the Magnetic Resonance Imaging Facility, Manchester Wellcome Trust Clinical Research Facility. The ADD study was funded via a project grant was awarded by the Efficacy and Mechanism Evaluation (EME) Programme and is funded by the Medical Research Council (MRC) and managed by the National Institute for Health Research (NIHR) on behalf of the MRC-NIHR partnership, and is sponsored by Northumberland and Tyne and Wear NHS Foundation Trust.
**TC13**

**THE TRANSCRIPTIONAL IMPACT OF IFN-ALPHA ON INFLAMMATORY, STRESS AND NEUROPLASTICITY GENES: RELATIONSHIP WITH DEPRESSION**

**Borsini A**
Psychological Medicine, Inst of Psychiatry, King’s College London, James Black Centre, 125 Coldharbour Lane, London, SE5 9NU, alessandra.borsini@kcl.ac.uk

Cattaneo A(1), Hepgul N(2), Russell A(1), Zajkowska Z(1), Zunszain PA(1), Pariante CM(1) (1)Dept of Psychological Medicine, Inst of Psychiatry, King’s College London, James Black Centre, 125 Coldharbour Lane,SE5 9NU, London (2) Health Service and Population Research Dept, King’s College London, Inst of Psychiatry, David Goldberg Centre, De Crespigny Park, SE5 8AF

Introduction: Interferon-alpha (IFN-α) is the standard treatment for chronic hepatitis C virus infection, which causes high rates of depression. However, little is known about the transcriptional impact of IFN-α in vivo and its relationship to behavioural changes. The study aims at investigating whether IFN-α administration caused alterations in the expression of inflammatory, neuroplasticity and stress genes in patients with and without IFN-α-induced-depression. Method: We recruited 58 HCV patients undergoing IFN-α therapy. The Mini International Neuropsychiatric Interview (MINI) was administered at baseline (treatment week (TW) 0) and throughout the treatment for diagnosis of depression. Blood samples were collected using PAXgene Blood RNA Tubes at TW0, TW4 and at TW24. For gene expression we selected the inflammatory candidate genes interleukin-4 (IL-4) and IL-17; brain-derived neurotrophic factor (BDNF) as indicator of neuroplasticity; and the glucocorticoid nuclear receptor (NR3C1) as related to stress response. Results: At TW0, IL-4 (p=0.01, +5%) and IL-17 (p<0.0001, +17%) were differently expressed in depressed when compared with non-depressed, however no significant differences were reported in the level of BDNF (p=0.82, 1%) and NR3C1 (p=0.15, -5%). When comparing TW4 with TW0, IL-4 and IL-17 were significantly down-regulated in depressed (p=0.01, -10%; p<0.0001, -20%, respectively), but not in non-depressed (p=0.98, 0%; p=0.23, -5%, respectively). NR3C1 was significantly decreased in both groups (p=0.04, -10%; p<0.0001, -13%, respectively). Finally, when comparing TW24 with TW0, IL-4 and IL-17 were significantly down-regulated in depressed (p=0.01, -4%; p<0.0001, -20%, respectively), but not in non-depressed (p=0.96, 0%; p=0.39, -30%, respectively). Contrarily, BDNF was significantly decreased in non-depressed, but not in depressed (p=0.04, -5%; p=0.23, -2%, respectively). NR3C1 levels were significantly decreased in both depressed and non-depressed (p=0.04, -7%; p<0.05, -12%, respectively). Conclusion: Our findings support the presence of a dysregulation in inflammatory and neuroplasticity genes involved in the development of IFN-α-induced depression. This work was supported by the Medical Research Council (UK) MR/J002739/1, the Commission of European Communities Seventh Framework Programme (Collaborative Project Grant Agreement no. 22963, Mood Inflame) and the NIHR Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King’s College London.

**TC14**

**SALIVARY CORTISOL RESPONSE TO INFANT DISTRESS IS EXAGGERATED IN DEPRESSED PREGNANT WOMEN**

**Braithwaite EC**
Psychiatry Univ of Oxford, Warneford Hospital Oxford OX3 7JX elizabeth.braithwaite@psych.ox.ac.uk

Murphy ES(1), Ramchandani PG(2) (1)Dept of Psychiatry, Warneford Hospital, Oxford, OX3 7JX (2)Academic Unit of Child and Adolescent Psychiatry,3rd Floor, QWQM Bldg, Imperial College, St Mary’s Campus, London, W2 1PG

Introduction: The hypothalamic-pituitary-adrenal (HPA) axis has been proposed as a potential underlying mechanism which links maternal prenatal depression with adverse offspring outcomes. However, it is currently unknown whether the reactivity of the HPA axis to stress is altered in pregnant women who experience symptoms of depression. The aim of this research is to investigate whether the cortisol response to a distressed infant stimulus is enhanced in pregnant women with symptoms of depression compared with non-depressed controls. Methods: Salivary cortisol responses and subjective mood responses to the infant distress stimulus were measured in 53 primiparous late first trimester women. Results: Both groups showed a similar increase in state anxiety in response to the film (F(1,51)=42.2, p<0.001). However, there was a significant group difference in cortisol response to the film: the group of pregnant women with symptoms of depression showed a significant increase in salivary cortisol, whereas the control group did not (F(1,51)=8.23, p<0.006). Conclusion: Depression during pregnancy is associated with increased reactivity of the HPA axis. This finding is consistent with altered HPA functioning as a key mechanism linking prenatal mood disturbance and altered fetal development. This study was supported by the John Fell Fund. Elizabeth C Braithwaite is supported by a UK Medical Research Council Studentship (MR/J500501/1) Susannah Murphy is supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre based at Oxford University Hospitals Trust Oxford University.

**TC15**

**EXPOSURE TO MATERNAL CHILDHOOD ABUSE AND DEPRESSION IN UTERO: EFFECTS ON NEONATAL BEHAVIOURAL REGULATION AND THE HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS**

**Fantini E**
Psychological Medicine, King’s College London, De Crespigny Park London, SE5 8D enrica.fantini@kcl.ac.uk

Pawlby S(1), Conroy S(1), Osborne S(1), Zunszain P(1), Pariante C(1) (1) Div of Psychological Medicine, Inst of Psychiatry, King’s College London, De Crespigny Park, London SE5 8D

Introduction: Childhood abuse (CA) predicts depression in vulnerable periods (Bifulco A, et al. 2002. Bulletin of the Menninger Clinic: 66, 241–258). Depression (MDD) in pregnancy is associated with poor neonatal outcome (Field T, et al. 2006. Infant Behaviour & Development: 29, 445–455). We examine the effect of exposure to maternal CA and to antenatal MDD on neonatal regulatory behaviour. Methods: 66 women were assessed at 25-weeks’ gestation for MDD (SCID-I) and CA (CECA-Q). Offspring behaviour was assessed at 6-days-postpartum with the Neonatal
ABSTRACTS

Behavioral Assessment Scale (NBAS). Neonatal salivary cortisol was measured before and after the assessment. Results: 55 neonates were assessed with the NBAS (15 offspring of mothers with neither MDD nor CA; 10 offspring of mothers with MDD only; 8 offspring of mothers with CA only; 22 offspring of mothers with MDD and CA). Group differences were found in the NBAS scores (alertness: K-W(3)=13.40, p=.004; irritability: K-W(3)=8.24, p=.04). Compared with offspring of CA only mothers, those with MDD only mothers were less alert (z=2.89; p<.05) and more irritable (z=2.22; p<.05); likewise, offspring of mothers with MDD and CA were less alert (z=3.47; p<.05) and more irritable (z=2.52; p<.05). By contrast therefore, compared with the offspring of mothers with MDD, with or without CA, the offspring of mothers with CA only were more alert and less irritable. No differences were found in the NBAS scores of offspring of mothers with neither MDD nor CA compared with the other groups. Difficulties in neonatal regulatory behaviour were significantly correlated with increased cortisol levels following the NBAS (alertness: r=-.41, p=.002; irritability: r=.39, p=.005). Conclusions: Exposure to MDD with or without the added insult of maternal CA is associated with suboptimal neonatal behaviour. Offspring exposed to maternal CA only had high alert and low irritability scores. This suggests that compared to offspring exposed to MDD in utero, neonates exposed to maternal CA only are over-regulated. Neonatal sub-optimal regulatory difficulties are associated with increased HPA axis activity following the stress of being handled, whereas over-regulation is associated with lower HPA axis activity. Sources of financial sponsorship of the study: Foundation for the Study of Infant Death; South London Clinical Research Network Contingency Funding

TC16

IMPACT OF CHILDHOOD ADVERSITY ON HPA AXIS FUNCTION IN TREATMENT RESISTANT DEPRESSION

Jones BDM, Medicine, St. George’s Univ School of Medicine, Drill Hall, Northumberland Rd, NE1 8ST, jones.bdm@gmail.com

Introduction: It can be hypothesised that changes in the regulation of the HPA axis in response to childhood adversity may mediate an increased risk of chronic and/or treatment resistant depression (TRD). We sought to examine this in a population of TRD subjects who participated in an RCT of metyrapone McAllister – Williams et al. 2013 BMC Psychiatry Apr 3;13(1):205. Methods: 165 patients with moderate to severe treatment resistant depression were recruited from primary and secondary care. In all participants, the HPA-axis was assessed at baseline using the CAR measured at 0, 15, 30, 45, and 60 minutes post awakening. Saliva was collected by passive drool and was assayed by Salimetrics. The CAR was assessed by measures of total output (AUCg) and measures of reactivity (AUCi). Childhood trauma was assessed using the childhood trauma questionnaire (CTQ). Statistical analysis used Pearson’s correlations and T-test analysis. Results: The final analysis looked at controls n=42 vs. patients n=102. The controls and the patients did not differ in their mean CAR (AUCg or AUCi) p=0.232, p=0.848 but did however differ in the 11pm cortisol measurement p=0.024 (control:0.015 µg/dL, patients:0.064 µg/dL). As expected, the depressed patients had significantly greater total amount of childhood trauma in all 5 subcategories. In controls a higher CAR output (AUCg mean: 1.34 µg/dL) (R=0.367, p=0.020) as well as CAR reactivity (AUCi mean: 0.274 µg/dL) (R=0.315, p=0.048) was associated with childhood trauma, in particular emotional neglect. In patients, AUCg (mean:1.12 µg/dL) R=0.202, p=0.042 but not AUCi (mean:0.256 µg/dL) R=0.067, p=0.501 was associated with emotional neglect. No other measures of the CTQ correlated with the CAR. In the whole group, there was a trend for AUCg to correlate with emotional neglect (r=0.154, p=0.067). Conclusion: The results suggest that there is no difference in the CAR among treatment resistant depressed patients and healthy controls, however 11pm cortisol was significantly higher in patients than controls. Childhood adversity appeared to be increased in the TRD population and, for emotional neglect, was associated with increased cortisol output. Trial Registration The study was registered on 21/12/2009 (ISRCTN45338259) under the title “Antiglucocorticoid augmentation of antiDepressants in Depression: the ADD study”. Funding details This study was funded by NIHR EME (funder’s reference 08/43/39).

TC17

CORTICOSTEROID RECEPTOR FUNCTION AND NEUROPSYCHOLOGICAL PERFORMANCE IN HEALTHY CONTROLS AND EUTHYMIC PATIENTS WITH BIPOLAR DISORDER

Clark JE, Academic Psychiatry, Newcastle Univ, Wolfson Research Centre, Campus for Ageing and Vitality, Newcastle upon Tyne NE4 5PL, j.e.clark1990@gmail.com
Gallagher P(1), Ferrier IN(2), Bulmer SJ(2), Preston S(3), Adams T(2), Watson S(2) (1)Inst of Neuroscience, Newcastle Univ, The Henry Wellcome Bldg, Framlington Place, Newcastle upon Tyne, NE2 4HH, UK (2) Academic Psychiatry and Regional Affective Disorders Service, Newcastle Univ, Wolfson Research Centre, Campus for Ageing and Vitality, Newcastle upon Tyne, NE4 5PL, UK (3) Inst of Brain, Behaviour & Mental Health, Faculty of Medical and Human Sciences, Oxford Rd, Manchester, M13 9PL

Introduction: Alteration of mineralocorticoid receptor (MR) and/or glucocorticoid receptor (GR) function has been implicated in the pathophysiology of bipolar disorder and may contribute to neuropsychological impairment. We examined MR and GR function using neuroendocrine and neuropsychological techniques and compared receptors in euthymic bipolar patients and healthy controls. On the basis of animal and human data we hypothesised that patients would have reduced GR function and normal or enhanced MR function. Method: Eighteen euthymic male bipolar patients and eighteen healthy male controls were recruited. On three separate occasions (at 14:00h), participants received either 0.5 mg dexamethasone or 0.5mg fludrocortisone or placebo, in a balanced randomised double-blind order. A two-week washout period followed each administration. At every visit, clinical data was collected and neuropsychological performance on tests of spatial working memory, attention and delayed verbal recognition was assessed. Plasma and saliva samples for cortisol were collected that afternoon and the following morning (findings submitted separately (BAP abstract, Douglas 2014)). Data was analysed using ANOVA and regression modelling with a p value of .05. Results: Patients made significantly more between-search errors overall in the CANTAB spatial working memory task (p<.01) and their performance after fludrocortisone
was associated with the degree of cortisol suppression ($r = .54, p < .05$). Patients' performance after placebo ($p < .05$) and fludrocortisone ($p < .01$) on the spatial only memory task (Kessels' Paradigm) was impaired compared to controls but after dexamethasone treatment, performance improved and was comparable to controls. On the word learning task, recognition memory was impaired in patients ($p < .05$) and was related to self-reported emotional abuse ($r = .51, p < .05$). In both groups fludrocortisone improved recognition ($p < .05$). The impact of MR and GR function on emotional bias in verbal recognition was examined. Fludrocortisone impaired controls' ability to correctly identify positive foils ($p < .05$). This effect was seen for both fludrocortisone ($p < .05$) and dexamethasone ($p < .05$) in the patient sample. Dexamethasone treatment resulted in a trend towards enhanced identification of negative foils in patients ($p = .05$). Conclusion: Blood results showed the degree of cortisol suppression induced by dexamethasone and fludrocortisone was comparable in patients and controls. However, neuropsychological data show that dexamethasone and fludrocortisone differentially impact performance in patients and controls. This indicates differences in the cognitive effects of corticosteroid receptor agonists in patients and healthy controls and may suggest their receptors are involved, at least in part, in the pathogenesis of cognitive dysfunction in bipolar disorder. This study received funding from the Northumberland, Tyne and Wear NHS Trust.

**TC18**

**MINERALOCORTICOID RECEPTOR FUNCTION IN BIPOLAR DISORDER**

*Clark JE, ION, Newcastle Univ, Wolfson Research Unit, CA V, Newcastle, NE4 5PL p.douglas@newcastle.ac.uk*

Douglas P, Clark JE, Gallagher P, Preston S, Ferrier IN, Watson S ION, Wolfson Research Unit, CAV, Newcastle, NE4 5PL

Introduction: The hypothalamic-adrenal-pituitary (HPA) axis is partially modulated by negative feedback of cortisol via mineralocorticoid receptors (MR) and glucocorticoid receptors (GR). To our knowledge, there are no other studies examining the function of the MR receptor using an MR agonist in bipolar patients. We propose that MR function can be estimated in vivo using endocrine techniques, and that MR function will be normal or upregulated in bipolar patients in comparison to healthy controls. Methods: 36 male subjects (18 remitted bipolar patients, 18 healthy controls) were recruited. The study medications were dexamethasone 0.5mg, fludrocortisone 0.5mg and placebo. Participants were given treatments in random order over three visits in a double blinded study with a 2 week washout period between treatments. On Day 1, a venflon was introduced at 13:00. Study medication was administered at 14:00. Plasma cortisol was measured at 30 minute intervals from 13:00 to 20:00. Neuropsychological assessment was carried out in the afternoon and is presented separately (Clark et. al, submitted to BAP Summer Meeting 2014). On Day 2, 5 salivary cortisol samples were taken from awakening to examine the cortisol awakening response (CAR). Area under the curve with respect to ground (AUCg) and respect to increase (AUCi) was calculated for plasma and salivary cortisol. Regression modelling was conducted to examine the relationships between outcomes in each group. Results: The plasma cortisol AUCg was lower for both healthy controls and bipolar patients after dexamethasone ($p < 0.01$) and fludrocortisone ($p < 0.01$) (compared with placebo). Both groups also demonstrated lower CAR after dexamethasone ($p < 0.001$) but not fludrocortisone. There was no between subject effect, nor drug by group interaction. In controls, plasma cortisol decreased linearly with time ($p < 0.05$), whereas patient data fit both linear ($p < 0.001$) and cubic ($p < 0.001$) models. In controls CAR followed a quadratic trend with time ($p < 0.01$) whilst time had no effect in patients. We found that plasma response to dexamethasone and fludrocortisone correlated in controls ($r = 0.50$, $p < 0.05$) but not patients, though plasma measures after fludrocortisone and placebo were highly related in patients ($r = 0.57$, $p < 0.05$). Conclusions: Euthymic bipolar patients and controls had comparable HPA axis function as measured by plasma and salivary cortisol after dexamethasone and fludrocortisone administration, though there was evidence of subtle differences between groups. The endocrinological data alone is insufficient to suggest HPA axis dysregulation in remitted bipolar patients but this should be examined in conjunction with the neuropsychological data to further understand MR and GR functionality. Funding from NTW Foundation Trust

**TC19**

**HAIR CORTISOL: A BIOMARKER FOR MOOD AND ANXIETY DISORDERS?**

*Herane Vives A, Psychological Medicine, King's College London, 103 Denmark Hill, SE5 8AF andres.herane@kcl.ac.uk*

de Angel V(2), Wise T(1), Arnone D(1), Papadopoulos A(1), Young A(1) Cleare A(1) King’s College London, Inst of Psychiatry, Dept of Psychological Medicine, Section of Neurobiology of Mood Disorders, 103 Denmark Hill London SE5 8AZ (2) Unidad de trastornos del Animo, Clínica Psiquiátrica Universitaria, Universidad de Chile, Av La paz 1003, Santiago de Chile

Background: Abnormal stress response is thought to be involved in the neurobiology of several psychiatric disorders. - Cortisol, the ‘stress hormone’, has the potential to be used as a biomarker for certain disorders as they are thought to have different patterns of cortisol secretion. However, current methods of assessment can only assess acute levels of cortisol. - Measuring cortisol in hair offers the possibility of averaging out cortisol levels within defined time-periods, providing a measure of chronic levels of this hormone and offering a “window” into the past. Thus, this novel, non-invasive paradigm could enhance our understanding of the relationship between stress, cortisol and related psychiatric disorders. Methods: Databases searched: In order to identify studies relevant to the aims outlined, a systematic search was conducted. Terms to cover hair cortisol, stress and psychiatric disorders were combined. Reviews (n=8) and animal studies were immediately excluded, resulting in a total of 63 primary research papers, letters and conference abstracts. The articles were individually scanned to elaborate whether they fulfilled the following requirements: a) research was in humans b) the study used scalp hair from the posterior vertex c) information was provided about the sampling and cortisol extraction methods used and d) focus was on the assessment of stress and/or mental health. Reviewing the full text of the 63 articles resulted in the identification of 21 relevant studies. Results: Articles on stress related conditions (11) generally showed that a wide variety of stressors increased cortisol concentrations in hair even if that association was not reflected in psychological scales. Articles on psychiatric disorders (10): Studies which showed that levels of hair cortisol concentrations in cases (vs. controls) were: Lower : General Anxiety Disorder (GAD), PTSD, Childhood trauma. Higher : PTSD, Alcoholism, Major depression (MDD), Heavy MDMA users. No difference: Bipolar disorder, MDD with comorbid coronary heart disease One study on PTSD showed high levels of cortisol at the time of the traumatic event and low levels 3 months after the event. Conclusions: 1. All studies assessing the effects of
stress on hair cortisol showed an increase in cortisol levels. Thus, this offers an objective method for assessing retrospectively the biological effects of stressors. 2. Hair cortisol levels provide a potentially more reliable indicator of long-term levels of cortisol. 3. The relationship between acute measures of cortisol such as salivary levels and chronic measures such as hair cortisol remains to be established. The combination of acute and chronic measures of cortisol could translate to a more refined and specific assessment of HPA axis changes in relation to different psychiatric conditions. 4. The establishment of hair cortisol as a biomarker would have the potential to help improve the diagnostic validity or sub-typing of psychiatric disorders. The author declares that he has no conflicts of interests and does not receive any financial sponsorship.

TC20
GENE EXPRESSION PROFILES ASSOCIATED WITH INTERFERON-ALPHA-INDUCED DEPRESSION
Hepgul N, Health Services and Population Studies, Inst of Psychiatry, King’s College London, Room H1.16, David Goldberg Bldg, London, SE5 8AF nilay.hepgul@kcl.ac.uk
Cattaneo A(1), Russell R(1), Borsini A(1), Mondelli V(1), Hotopf M(1), Pariante CM(1). (1) Dept of Psychological Medicine, Inst of Psychiatry, King’s College London, SE5 9NU

Interferon-alpha (IFN-α) treatment for chronic hepatitis C virus infection is known to cause major depression in up to 45% of subjects (Amis & De la Garza, 2006, J. Clin. Gastroenterol, 40, 322-35; Raison et al, 2005, CNS Drugs, 19, 105-123). However, the biological mechanisms through which IFN-α treatment causes depression are still not clear. An emerging and useful method to investigate the pathogenesis of depression is the use of peripheral blood to measure the expression levels of genes. Only a few studies have employed this technique in IFN-α-induced depression. The aim of this study is to investigate baseline gene expression differences as well as IFN-α-induced changes in gene expression, and their contribution to the development of IFN-α-induced depression. 58 patients with chronic hepatitis C virus infection were assessed using a prospective cohort design; at baseline and at each month of IFN-α therapy. New onset cases of depression during IFN-α therapy were determined using the Mini International Psychiatric Interview (MINI). Blood samples were collected at baseline and treatment week 4 (TW4) using PAXgene Blood RNA Tubes and gene expression microarray assays were performed using Affymetrix® Human Gene 1.1 ST Array strips. Pathway analyses were run using Ariadne Pathway Studio Software. 21 (36%) patients developed IFN-α-induced depression during the 24-week course of therapy, while 37 patients (64%) did not. At baseline 56 genes were differentially expressed in patients who later developed IFN-α-induced depression compared to those who did not. Of relevance to depression this included higher expression of eukaryotic translation initiation factor 4B (EIF4B) and growth arrest-specific 5 (GAS5), and lower expression of insulin-like growth factor binding protein 7 (IGFBP7) in the depressed group. At TW4, 747 genes were modulated by IFN-α in patients with IFN-α-induced depression and 315 genes in patients without IFN-α-induced depression. Further analysis revealed 258 genes to be in common between the two groups of patients whereas 489 genes were modulated only in patients with IFN-α-induced depression, and 57 genes were modulated only in patients without IFN-α-induced depression. Pathway analyses in the depressed group identified alterations in 21 pathways including interleukin-6 (IL-6), interleukin-10 (IL-10) and extracellular-signal-regulated kinase 5 (ERK5) signalling pathways. Our data suggests patients who develop IFN-α-induced depression have an increased biological sensitivity to IFN-α and differential modulation of inflammatory and neuroplasticity related pathways. This research was funded by the Medical Research Council and by the Commission of European Communities Seventh Framework Programme (Collaborative Project Grant Agreement no. 22963, Mood Inflame).

TC21
INvolvement of the endocannabinoid system in interferon-alpha (IFN-α) induced depression: A gene expression study
Zajkowska Z, Psychological Medicine, Inst of Psychiatry, James Black Centre, CCBB 125 Coldharbour Lane, London, SE5 9NU, zuzanna.zajkowska@kcl.ac.uk

The endocannabinoid (eCB) system exhibits neuromodulatory properties that have been implicated in mood regulation. In particular, deficiencies in eCB signaling have been linked to depression. In the present study we investigated whether genes belonging to the eCB system are involved in mechanisms underlying depression development upon interferon-alpha (IFN-α) treatment, received by patients with chronic hepatitis C (HCV) viral infection. We focused on four genes: CNR2, coding for CB2, one of the main eCB receptors that regulates neuronal signaling and inflammatory response through its inhibitory functions; NAPE-PLD and DAGL, coding for enzymes involved in eCB synthesis, and FAAH, coding for a degrading eCB enzyme (Zajkowska et al., Pharmacogenomics, in press). We recruited 50 HCV patients receiving IFN-α treatment and assessed them at treatment weeks 0, 4 and 24. We evaluated depression by using the M.I.N.I. International Neuropsychiatric Interview and analysed mRNA levels using Affymetrix® Human Gene 1.1ST Array. Our results show that NAPE-PLD and DAGL-α, an isoform of DAGL, were lower at baseline in those patients who developed depression vs those who did not (-17%, p=0.02; -17%, p=0.003; respectively). After 4 weeks of treatment, levels of CNR2 were reduced (-21%, p=0.001), while levels of FAAH2, an isoform of FAAH, and DAGL-α were increased in the whole sample compared to baseline levels (+19%, p=0.01, +19%, p<0.001, respectively). After controlling for depression development, FAAH2 levels were significantly increased in depressed patients only (+25%, p=0.005). From baseline to week 24, CNR2 levels decreased in non-depressed patients (-29%, p<0.001). Interestingly, at week 24 CNR2 levels were higher in depressed compared with non-depressed individuals (+27%, p=0.001). Our findings suggest that alterations in the expression of the genes of the eCB system might underlie the increased vulnerability for depression development in HCV infected patients treated with IFN-α. This work was supported by the Medical Research Council (UK) MR/J002739/1, the Commission of European Communities Seventh Framework Programme (Collaborative Project Grant Agreement no. 22963, Mood Inflame) and the NIHR Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King’s College London.
OLANZAPINE CLEARANCE INCREASED BY SERTRALINE CO-ADMINISTRATION IN PEOPLE WITH PSYCHOTIC DEPRESSION. A POPULATION PHARMACOKINETIC ANALYSIS

Davies SJC, Geriatric Psychiatry Division, CAMH/Univ of Toronto, 6th Floor, 80 Workman Way, Toronto, Ontario, Canada, M6J 1H4, simon.davies@bristol.ac.uk
Pollock BG(1, 2), Kirshner M(3), Meyers BS(4), Flint AJ(2, 5), Rothschild AJ(6), Whyte EM(3), Sorisio D(3), Mulsant BH(1, 2), Bies RR (1, 7), for the STOP-PD study group. (1) Centre for Addiction and Mental Health, Toronto, Canada (2) Dept of Psychiatry, Univ of Toronto, Canadian (3) Univ of Pittsburgh Medical Center, Pittsburgh, USA (4) Weill Medical College of Cornell Univ & New York Presbyterian Hospital, USA (5) Dept of Psychiatry, Univ Health Network, Toronto, Canada, (6) Univ of Massachusetts Medical School and Memorial Health Care, Worcester, USA (7) Indiana Univ School of Medicine, Indianapolis, USA

Clinical evidence and expert opinion support the use of the combination of an antipsychotic and antidepressant in the treatment of major depression with psychotic features. We characterized the impact of sertraline co-administration on the clearance of olanzapine in patients with psychotic depression using population based pharmacokinetic (PPK) methods. We analyzed data from the Study of Pharmacotherapy for Psychotic Depression (STOP-PD) that randomized 259 younger and older participants to either olanzapine plus placebo or olanzapine plus sertraline. Olanzapine was started at 5 mg/day (2.5 mg for frail elderly patients) and sertraline at 50 mg/day (25 mg for frail elderly patients). Doses were increased every 3 days and could be adjusted based on response and tolerability up to 20 mg/day for olanzapine and 200 mg/day for sertraline. Concentration samples for olanzapine were collected at study visits on up to two occasions during the 12-week trial and additionally in the stabilization phase which continued for a further 12 weeks. The population pharmacokinetics of olanzapine were analyzed using nonlinear mixed effect modeling software, NONMEM, Version VII. The effects of the following covariates were assessed: sex, race, smoking, age, and sertraline co-administration. The PPK analysis comprised 335 olanzapine concentration samples from 175 individuals (67.6% of study participants). The structural model published by Bigos et al [1] was sufficient to describe the olanzapine data in the study adequately. This was a one-compartment model with first order absorption and elimination, using an additive and proportional residual error structure. The absorption rate constant (Ka) was fixed to 0.5 based on the Bigos et al model [1]. Sertraline co-administration significantly increased olanzapine apparent clearance (chi-square =10, df=1 p<0.005); the increase ranged from 12% to 29% depending on the patient characteristics included in the model. Older age was related to a decrease in clearance with a 31% reduction from 30 to 75 years of age (p<0.005). Male sex and African-American race/ethnicity were associated with increased clearance but the smoking covariate was not identifiable in this dataset (p>0.05). Contrary to our expectations from knowledge of cytochrome p450 interactions [2], olanzapine clearance increased in the presence of sertraline. This effect might be explained by sertraline inhibiting the p-glycoprotein transporter or by lower olanzapine adherence in patients treated with sertraline. [1] Bigos KL et al. Mol Psychiatry. 2011;16:620-5. [2] Flockhart D. http://medicine.iupui.edu/climpfhm/DDIS/ Funding: Grants; US Public Health Service, NIMH, National Center for Research Resources. Eli Lilly and Pfizer donated olanzapine, sertraline, placebo.

IN VITRO EFFECT OF ANTIDEPRESSANTS AND OMEGA-3 FATTY ACID IN IMPROVING THE IMPAIRED GR SENSITIVITY IN CHD PATIENTS WITH DEPRESSION

Nikkheslat N, Dept of Psychological Medicine, Inst of Psychiatry, King’s College London, Section of Stress, Psychiatry and Immunology (SPI-Lab), The James Black Centre, Room 2-059, 125 Coldharbour Lane, London SE5 9NU, naghmeh.nikkheslat@kcl.ac.uk
Nikkheslat (1,2), Zumszain PA(1), Barbosa IG(1), Tylee AT(4), Carvalho LA(3), Pariante CM(1) (1) Inst of Psychiatry, King’s College London, The James Black Centre, 125 Coldharbour Lane, London SE5 9NU (2) Univ of Roehampton, Holybourne Ave, London SW15 4JD (3) Univ College London.1-19 Torrington Place, London WC1E 7HB (4)Health Service and Population Research Dept, Inst of Psychiatry, King’s College London.

Introduction: Coronary heart disease (CHD) and depression are common and often co-existing disorders. Depression exacerbates adverse cardiac outcomes in CHD patients, increasing the risk of cardiovascular morbidity and mortality, besides worsening the psychological and social morbidity (Miller et al., 2002, The American Journal of Cardiology, 90:1279-1283). Inflammation has been recognised to be involved in the association between these two debilitating disorders (Halaris, 2013, Current Psychiatry Reports, 15:400). Therefore, failure of regulatory mechanisms in the control of inflammation could be particularly important in the development of depression in CHD patients (Davidson, 2012, ISRN Cardiology, 2012:743813). One of the important biological factors that regulate inflammation is the glucocorticoid receptor (GR), so this project aims to investigate the inflammatory response and to evaluate the function of GR in CHD patients with and without depression. Methods: CHD patients with (n=28) and without (n=55) depression were recruited. Depression status was assessed by means of CISR (Clinical Interview Schedule revised) for diagnosis of depression, and Beck depression inventory for the presence of depressive symptoms. Serum CRP and plasma VEGF were measured using commercially available ELISA kits. Gene expression of IL-6 was measured via qPCR. GR sensitivity was measured in vitro on isolated peripheral blood mononuclear cells using the dexamethasone inhibition of lipopolysaccharide-stimulated Interleukine-6 production method. Results: Compared to CHD non-depressed individuals, CHD patients with depression showed higher serum levels of CRP (5.20 vs 3.34 mg/l, p=0.030), higher gene expression of IL-6 (2.8 fold increase, p=0.003), and higher plasma levels of VEGF (173.13 vs 94.24 pg/ml, p=0.028). The depressed group exhibited reduced GR function (IC50: 8.12 vs 7.59 [M], p=0.0031) which was associated with the severity of depression (r=0.505, p=0.006). CHD depressed subjects showed an increased in GR sensitivity by the in vitro effect of clomipramine (IC50: 7.54 vs 7.81 [M], p=0.084), citalopram (IC50: 7.57 vs 8.06 [M], p=0.014), and the omega-3 fatty acid EPA (IC50: 7.43 vs 8.61 [M], p=0.006). Conclusions: In CHD patients, depression was accompanied by elevated levels of inflammation in the context of GR resistance. This study provides evidence of improvement of GR functional responsiveness in vitro in response to the effect of antidepressants as well as Omega-3 fatty acids that may lead to a more effective response to the anti-inflammatory and immunosuppressive activities of glucocorticoids. This study was supported by EU-FP7-HEALTH-F2-2008-222963 “MOODINFLAME”; British Council-Partek Partnership; Biomedical Research Council, King’s College London; and ECNP Young Investigator Award to Dr. Livia A Carvalho.
TC24

COMBINATION TREATMENT WITH BUPRENORPHINE/NALTREXONE, A FUNCTIONAL KAPPA OPIOID RECEPTOR ANTAGONIST, PRODUCES ANTIDEPRESSANT-LIKE EFFECTS IN MICE

Almatroudi AM, Dept of Pharmacy and Pharmacology, Univ of Bath, Claverton Down, Bath, BA2 7AY; amai21@bath.ac.uk
Husbands SM(1), Bailey CP (2), Bailey SJ (3) (1,2,3) Dept of Pharmacy and Pharmacology, Univ of Bath, BA2 7AY

Introduction: Antagonists at kappa-opioid receptors have been proposed as novel antidepressants. The standard high-affinity, selective kappa-antagonists have a long lasting duration of action which potentially limits their use (Carroll and Carlezon 2013. J Med Chem 56: 2178-2195). Buprenorphine is a partial mu-opioid receptor agonist and a kappa-antagonist, while naltrexone is a non-selective opioid antagonist. Buprenorphine (1mg/kg) administered in combination with naltrexone (1mg/kg) produced a functional short-acting kappa-antagonist that was non-sedating and non-nrewarding in mice. (Almatroudi et al. 2013. Proceedings of the British Pharmacological Society at https://bps.conference-services.net/resources/344/3654/pdf/PHARM13_0127.pdf). Here, we report the effects of this combination treatment on depression-related behaviours. Methods: CD-1 male mice, 8-9 weeks old (University of Bath) were used. For the forced swim test, animals were group housed (n=4) and randomly assigned to control (0.9% w/v saline) or drug-treated groups (n=10 per group). For novelty-induced hypophagia, mice were individually housed and trained for 3 days to consume condensed milk. On test days, mice were injected intraperitoneally (10 ml/kg) with saline, buprenorphine alone (1 mg/kg), naltrexone alone (1 mg/kg), buprenorphine/naltrexone combination (1 mg/kg) or fluoxetine (20 mg/kg) one hour prior to testing behaviour. In the forced swim test, a 6 min swim test session was recorded and behaviour scored manually. In the novelty-induced hypophagia test, the latency to drink and consumption were recorded in the home cage (day 4) and in the novel cage (day 5). Data were analysed using a one-way ANOVA, and least significant difference test (InVivo Stat software). Results: In the forced swim test, there was a significant effect of drug-treatment on swimming and immobility behaviours (swimming: F (5, 54) = 4.9, P<0.001; immobility: F (5, 54) = 5.7, P<0.001). Post-hoc testing revealed that fluoxetine and buprenorphine/naltrexone combination significantly reduced the time spent immobile, compared to controls (P<0.01). Interestingly, buprenorphine alone or naltrexone alone also reduced the time spent immobile (P<0.001). In the novelty-induced hypophagia test, there was a significant effect of drug treatment on the latency to drink in the novel cage (F (5, 54) = 8.5, P<0.001) but not consumption (F (5, 54) = 1, P=0.4). Both fluoxetine and buprenorphine/naltrexone significantly reduced the latency to drink in the novel cage compared with saline treated controls (P<0.05). Conclusion: The combination of buprenorphine/naltrexone produced antidepressant-like effects in the forced swim and novelty-induced hypophagia tests. Interestingly, the effects of the combination treatment were similar to either buprenorphine alone or naltrexone alone. We are investigating the extent to which mu- and kappa-opioid receptors may contribute to these behaviours. Supported by the government of Saudi Arabia

TC25

REFINEMENT OF THE RAT FORCED SWIM TEST AS A MODEL FOR DETECTING ANTIDEPRESSANT ACTIVITY

Bannerton K, Discipline of Pharmacology and Therapeutics, School of Medicine, National University of Ireland, Galway, CNS Lab, 000, k.bannerton1@nuigalway.ie
Kelly, JP (1) (1) Discipline of Pharmacology and Therapeutics, School of Medicine, National University of Ireland, Galway.

Although the rat forced swim test (FST) is extensively used for evaluating antidepressant efficacy, there are several caveats to consider in the interpretation of the results. For example, treatment is typically subacute (i.e. 3 doses over 24h), whilst clinically antidepressant efficacy requires chronic administration (analogous to 2 weeks of treatment in rodents). Furthermore, stimulant drugs are false positives in the test due to general locomotor activation. The scoring method for the principal behavioural indices (i.e. immobility, climbing and swimming) can also vary, either being scored continuously or in time bins. Thus, the aim of this study was to assess these three aspects by comparing the effects of subacute and chronic treatment with the tricyclic antidepressant desipramine (DMI, 10mg/kg, s.c.) and subacute treatment with the false positive amphetamine (AMP, 1mg/kg, s.c.) in young adult male Sprague-Dawley rats in the FST, using both continuous and time sampling scoring approaches. The FST involves two exposures to water-filled cylinders (23-25°C), the first 15 min exposure being followed 24h later by a 5 min exposure. All rats received 15 injections: 1 injection on days 1-13, and 2 injections on day 14 (5 and 1h prior to the second FST exposure). Control rats received 15 vehicle (distilled water) injections. For subacute treatment, rats received vehicle on days 1-12 and DMI or AMP at 24, 5 and 1h prior to the second FST exposure. Data were analysed using One-Way ANOVA, followed where appropriate by post hoc Student-Newman Keuls; p<0.05 was deemed statistically significant. Both subacute DMI and AMP, and chronic DMI significantly reduced immobility and increased climbing, whilst subacute AMP also significantly increased swimming, effects that were evident using both scoring methods, suggesting that either method is valid. In conclusion, this study demonstrated that the FST can be refined to detect antidepressant effects following a 14 day repeated dosing procedure, and a locomotor component can be incorporated that will identify false positives in the model. This study was funded internally by the Discipline of Pharmacology & Therapeutics, School of Medicine, NUI, Galway.
TC26

THE EFFECT OF REPEATED RESTRAINT STRESS AND SOCIAL ISOLATION ON JUDGEMENT OF AMBIGUOUS INFORMATION MEASURED USING A REWARD-BASED COGNITIVE AFFECTIVE BIAS TASK

Hales CA, School of Physiology and Pharmacology, Univ of Bristol, Medical Sciences Bldg, University Walk, Bristol, BS8 1TD, claire.hales@bristol.ac.uk

Houghton C(1), Robinson ESJ(2) (1) Dept of Computer Science, Univ of Bristol, Merchant Venturers Bldg, Woodland Road, Bristol, BS8 1UB (2) School of Physiology and Pharmacology, Univ of Bristol, Medical Sciences Bldg, University Walk, Bristol, BS8 1TD

Exposure to chronic stress is an important risk factor for depression (de Kloet et al, 2005 Nat Rev Neurosci 6;463-475). In rodents, chronic stress can cause negative cognitive biases in interpretation of ambiguous information associated with anticipation of reward or punishment (Harding et al., 2004 Nature 427(6972):312-312; Papciak et al., 2013 Behav Brain Res 256:305-310). Similar negative cognitive affective biases (CABs) are seen in patients with depression (Gotlib & Joormann, 2010 Ann Rev Clin Psychol, 6(1):285-312). This study investigated the effect of repeated restraint stress and social isolation (RS&SI) on CAB measured using a novel operant reward-based ambiguous cue interpretation task. Male litter-hooded rats were trained to discriminate between two distinct reference tones and make a response on the appropriate lever to obtain high value reward (four sugar pellets) or low value reward (one sugar pellet). Rats included in the analysis (10-months old) were split into control (n=5) or RS&SI (n=5) groups using baseline performance. RS&SI rats were individually housed and subjected to restraint stress (15mins/day, Mon-Fri) for three weeks. During this time and for three weeks following return to control cage enrichment and paired-housing conditions, twice weekly test sessions (where both reference tones and a midpoint ambiguous tone were presented) were used to measure CAB. Compared to baseline performance, RS&SI caused rats to make fewer responses to the ambiguous tone on the high reward lever over all six sessions analysed together, indicated by a significantly smaller area under the curve (AUC) compared to controls (t(8)=2.81, p=0.023; independent-samples t-test): a mean decrease in positive responding of 8.9±0.8%. Although not significant, inspection of performance on individual sessions suggests this negative bias does not appear immediately following onset of RS&SI, instead occurring one week later. Returning RS&SI rats to control conditions did not reverse this CAB, as over the six sessions post-RS&SI the AUC for responses made on the high reward lever was significantly smaller than for controls (t(8)=2.54, p=0.035; independent-samples t-test), corresponding to a mean reduction in positive responding of 10.5±1.0%. This study suggests RS&SI can negatively bias interpretation of ambiguous information in a CAB task using cues signalling reward-based outcomes of different magnitudes. This agrees with findings from previous studies showing that stress manipulations can cause negatives biases using cues associated with reward or punishment. These findings also suggest that CABs induced by stress may not be reversed following removal from stressful conditions. This study provides support for considering use of reward-based operant CAB tasks as more ethical alternatives to those previously used, as no aversive training methods are used. This study was funded by Wellcome Trust Doctoral Training Programme in Neural Dynamics.

TC27

DEVELOPING STRESS AND INFLAMMATION - BASED ANIMAL MODEL OF DEPRESSION TO STUDY THE ROLE OF THE IMMUNE SYSTEM IN THE DISEASE NEUROBIOLOGY AND PHARMACOTHERAPY

Musaelyan K, Neuroscience, IOP KCL, CCBB 125 Coldharbour Lane, London, SE5 NU, ksenia.musaelyan@kcl.ac.uk

Egeland MT (1), Zunszain PA(1), Pariante CM(1), Thuret S(1) and Fernandes C(2) (1) CCBB IOP 125 Coldharbour Lane London SE5 9NU (2) MRC SGDP 16 De Crespigny Park, London SE5 8AF

Recent research in depression neurobiology highlighted the role of the immune system and adult hippocampal neurogenesis as key players in disease onset and progression, as well as potential novel targets for antidepressant therapy (Lucassen et al, 2010 Eur Neuropsychopharmacol. 20 (1) 1-17). To investigate the role of the immune system activation and alterations in hippocampal neurogenesis in depression, a valid animal model is required. To develop such a model, we propose to combine exposure to inflammatory stimulus modelled by peripheral lipopolysaccharide (LPS) injection with an environmental stress-based model of depression - unpredictable chronic mild stress (UCMS) to achieve an immunologically-relevant depression-like phenotype. In a pilot experiment, we treated 8 weeks old male BALB/c mice with LPS (0.33 mg/kg i.p.) and subsequently exposed them to UCMS for 7 weeks. Each condition group was also treated with saline (Veh) or Fluoxetine (FLX 10mg/kg i.p. daily), N=12 for each treatment group. A control group was also injected with saline or fluoxetine but otherwise left undisturbed (CNTRL). Coat state deterioration score was used to monitor depressive-like phenotype during the UCMS. At the end of the UCMS paradigm a behavioural testing battery was employed to assess anxiety, anhedonia and learned helplessness behaviours. LPS and UCMS exposed mice displayed significant coat state deterioration (UCMS factor H(7)=37.5, p<0.0001) and locomotor hyperactivity in a novel arena (UCMS factor F(1,74) =20.8, p<0.0001). When coat state was assessed 4 days after the end of UCMS paradigm, the UCMS-only group already displayed signs of recovery with the coat deterioration score not significantly different from control levels, while animals exposed to both LPS and UCMS did not show improvement of the coat state at this time point. Fluoxetine treatment of the LPS and UCMS exposed group promoted recovery of the coat state with the coat deterioration score returning to control levels (Mean±SEM, N=6-12: CNTRL 0.58±0.16, UCMS 1.33±0.33, LPS+UCMS 1.92±0.2, LPS+UCMS+FLX 1.21±0.19). These preliminary results suggest that immune system activation by LPS may affect the trajectory of the recovery from UCMS exposure. This finding is in line with clinical data suggesting that inflammatory biomarkers in patients can predict treatment response to antidepressant therapy (O’Brien et al 2007 J Psychiatr Res 41 (3-4) 326-31). Future assessment of the neurobiological phenotype (corticosterone response to stress, peripheral cytokines and hippocampal neurogenesis) will allow us to further unravel the neurobiological basis of the observed behavioural changes. This project is funded by Janssen Pharmaceutica studentship.
THE EFFECT OF CHRONIC RESTRAINT STRESS ON DEPRESSION-RELATED BEHAVIOUR IN JUVENILE AND ADULT C57BL/6 MICE

Sadler AM, Dept. of Pharmacy and Pharmacology, Univ of Bath, Claverton Down, Bath, BA2 7AY, a.sadler@bath.ac.uk
Bailey SJ Dept of Pharmacy and Pharmacology, Univ of Bath, Bath, BA2 7AY

Depression is a prevalent condition in adolescents affecting up to 6% of 13-18 year olds (Masi et al., 2010, Expert Opin Pharmacother, 11:375-386). Treatment is inadequate as the use of antidepressant medication in adolescents is associated with poor efficacy and increased suicidal behaviour. As there are currently few animal models of adolescent depression, we are developing and validating a mouse model. This study aimed to investigate the behavioural effects of chronic restraint stress in the forced swim test (FST) in adult and juvenile C57BL/6 mice. Male C57BL/6 mice (University of Bath), aged 4 weeks (juveniles) or 9 weeks (adults), were randomised into stressed and non-stressed groups (n=8-12/group). Stressed mice underwent 3 days of restraint (2 hours/day) in a restraint device. Blood samples were taken from the tail vein before and after stress (Sadler and Bailey, 2013, Lab Anim, 4:316-319). Following restraint, all mice were tested in the forced swim test (6 minutes, 25°C). Test sessions were recorded, and time spent swimming and immobile in the last 4 minutes were scored by an experimenter blind to treatment. Levels of corticosterone in plasma were determined using an ELISA (IBL International). Behavioural data were analysed using unpaired t-tests, and corticosterone data were analysed using a repeated measures mixed model analysis (InVivoStat software). In both adult and juvenile mice, chronic restraint stress significantly increased corticosterone above baseline (P<0.001), confirming that restraint is stressful. In adult animals, restraint increased the time spent swimming, and decreased the time spent immobile in the FST compared with non-stressed controls (P<0.005). Stress also significantly increased the latency to first immobility (P<0.05). In juvenile animals, there was no significant difference between stressed and non-stressed mice on the time spent either swimming or immobile, or on the latency to first immobility. Chronic stress produced an antidepressant-like behaviour in the FST in adult C57BL/6 mice. C57BL/6 mice have been proposed to be stress-resistant (Savignac et al., 2011, Neuroscience, 192:524–536), although we have also found similar results in the FST in the stress-sensitive BALB/c strain (Sadler and Bailey, 2013, pA2 Online, 11 (3):Abstract 046P). The decrease in time spent immobile may reflect increasing resilience on exposure to repeated restraint stress. These data suggest that 3 days chronic restraint stress may not be suitable to model adolescent depression in C57BL/6 mice. This study was supported by a Medical Research Council Doctoral Training Grant (AMS) and an MRC In Vivo Strategic Skills Award (SJB).

EFFECTS OF ANXIOLYTIC AND DOPAMINERGIC DRUGS ON SUCCESSIVE NEGATIVE CONTRAST IN RATS

Phelps C, Physiology and Pharmacology, Univ of Bristol, Medical Sciences Bldg, University Walk, Bristol, BS8 1TD, caroline.phelps@bristol.ac.uk
Robinson E. Medical Sciences Bldg, University Walk, Bristol BS8 1TD

Enhanced sensitivity to loss and failure in humans is symptomatic of a negative affective state. This may be replicated in preclinical successive negative contrast (SNC) tests. These measure changes in animal’s behavioural response to decreases in quantitative or qualitative value of reward. Here an operant SNC task was used to investigate the influence of anxiolytic diazepam, psychostimulant amphetamine and dopamine receptor antagonist alpha-flupenthixol on the SNC effect in response to devalue of reward from 4 food pellets to 1 food pellet. 12 male Lister-hooded rats were trained to nose-poke in response to a light cue, presented after a fixed inter-trial interval, resulting in the delivery of four food pellets. Diazepam (0.3, 1mg/kg), amphetamine (0.1, 0.3mg/kg) or alpha-flupenthixol (0.1, 0.3mg/kg) were administered (t=-30min, i.p) on Tuesday (4 food pellet baseline session) and Friday (1 food pellet devalue session) using a fully counter-balanced study design. Response latencies, premature and omissions were recorded and analysed using a repeated measures ANOVA with SESSION as within-subjects factor and DOSE as between-subjects factor. Diazepam and amphetamine treatment significantly attenuated the devalue effect at a dose which did not alter performance under baseline conditions, there was a significant SESSION*DOSE interaction for correct latency for both drugs (F=4.613 p=0.021 and F=5.588 p=0.011 respectively). A significant SESSION*DOSE interaction was also found for collection latency (F=8.256 p=0.002) and percentage premature (F=25.460 p=0.000) following diazepam treatment, but there were no such interactions with amphetamine. Both 0.3mg/kg diazepam and 0.3mg/kg amphetamine significantly attenuated the devalue effect on correct latency in comparison to vehicle. 1.0mg/kg diazepam significantly increased collection latency and decreased percentage premature in baseline sessions and increased omissions in the devalue session. Amphetamine induced an increase in percentage premature responses that was significant at 0.3mg/kg. Alpha-flupenthixol treatment significantly potentiated the devalue effect on correct latency at 0.1mg/kg but had non-specific effects at 0.3mg/kg (increased correct latency in both baseline and devalue sessions with no significant devalue effect). A significant decrease in percentage premature in devalue sessions was observed at both 0.1 and 0.3mg/kg. There was a significant SESSION*DOSE interaction of percentage omissions (F=11.636 p=0.004) with a significant increase in omissions in the devalue session at both doses. There were no significant SESSION*DOSE interactions for the other recorded variables. These data suggest that diazepam and amphetamine selectively attenuate the devalue effect whilst alpha-flupenthixol increases it. From this it could be inferred that anxiolytics and dopamine signalling both contribute to the SNC effect. Funding for this work was provided by the BBSRC.
TC30

NEUROANATOMICAL PHENOTYPE OF THE OLFACTORY BULBECTOMIZED RAT MODEL OF DEPRESSION

Vernon AC. Neuroscience, King’s College London, Inst of Psychiatry, The James Black Centre, 125 Coldharbour Lane London, SE5 9NU, anthony.vernon@kcl.ac.uk
Westphal R(2), McAleavey Z(3), Kelly JP(3) (2)King’s College London, Inst of Psychiatry, Dept of Neuroimaging, De Crespigny Park, London SE5 8AF (3)National University of Ireland Galway, Galway Neuroscience Centre, Dept of Pharmacology

Olfactory bulbectomy (OBX) induces behavioural, endocrine and neurochemical deficits similar to depressed subjects. How OBX induces depressive-like symptomology, largely remains unanswered. Magnetic resonance imaging (MRI) studies of the depressed state have shown ventricular hypertrophy and decreased volume of the frontal lobe, caudate and amygdala (Kempton et al., 2011, Arch. Gen. Psych. 68: 675-90). We therefore investigated the extent of neuroanatomical abnormalities in OBX or sham-operated animals using ex-vivo structural MRI combined with automated unbiased tensor-based morphometry. Our study sample consisted of 9 male and 10 female sham-operated and 6 male and 8 female OBX-rats. The OBX surgery was performed as described previously (Roche et al. 2007, Neropsychopharmacology 32:1312-20). Samples were prepared for ex vivo MRI and T2-weighted, MR images acquired as described (Vernon et al., 2013, Biol. Psychiatry. in press). Morphometry was analysed using a voxel-based morphometry (VBM) framework implemented in SPM8 (Wellcome Department of Cognitive Neurology, London, UK). (Suzuki et al. 2014. Neuroimage 77:215-221). Statistical analysis between sham and OBX-rats was performed using a general linear model (GLM) with total brain volume and gender as covariates. False Discovery Rate (FDR) multiple comparison correction was applied to all statistical tests (threshold q<0.05). Due to the small sample size, we also conducted additional analysis at an exploratory threshold (p<0.05 uncorrected). OBX induced significant reductions in GM volume in the olfactory tubercle and piriform cortex. Significant WM reductions were observed in the medial forebrain bundle, anterior commissure and lateral olfactory tract (all q=0.05). Exploratory analysis (p<0.05 uncorrected) revealed widespread GM reductions frontal (infralimbic cortex), limbic (entorhinal cortex, amygdala, hippocampus) and motor (striatum) regions. A similar analysis for WM revealed extensive reductions in the cingulum, corpus callosum (forceps major) and optic tract. No ventricular hypertrophy was observed. OBX induces a distinct pattern of structural remodelling in the rat brain. Perhaps unsurprisingly, this primarily reflected decreased volume of GM regions linked to olfaction and WM tracts known to project from the rodent olfactory system. Exploratory analysis revealed widespread decreases in GM and WM, which overlap with neuroanatomical abnormalities in depressed patients and prior neuropsychological studies in OBX rats. These preliminary data suggest the OBX model recapitulates at least some neuroanatomical features of the depressed state, increasing its face validity as a model system. Further investigations are now underway to relate these neuroanatomical changes to depressive-like behaviour in OBX rats and to understand the underlying neurobiology. Funding from the Psychiatry Research Trust awarded to ACV (Grant ID: McGregor 97) whom we thank for their generous financial assistance supported this study. The authors also thank the British Heart Foundation for supporting the 7T MRI scanner at the King’s College London Preclinical imaging unit (KCLPIU).

TC31

DO SUB-REGIONS OF THE MARMOSE MEDIAL PFC DIFFERENTIALLY REGULATE A NEGATIVE EMOTIONAL RESPONSE?

Wallis C. PDN, Univ of Cambridge, Downing St, Cambridge, CB2 3EG, cuw20@cam.ac.uk
Roberts A (1), Clarke H (1) Physiology, Development and Neuroscience, Univ of Cambridge, Downing St, Cambridge CB2 3EG

There is strong evidence that the human medial prefrontal cortex (mPFC) is important for emotion regulation. Abnormal activity in the mPFC has consistently been associated with disorders of negative emotion (anxiety and depression), and its reversal is associated with successful treatment response (Drevets et al 1997, Nature 386(6627):824-7; Mayberg et al 2000, Biological psychiatry 48(8):830-43). However, there is uncertainty regarding the contribution of distinct subregions of the primate mPFC to negative emotion regulation (Myers-Schulz and Koenigs 2012, Molecular psychiatry 17(2):132-41). The aim of the present work is therefore to investigate the contribution of areas 25 and 32 of the mPFC to negative emotion regulation in the common marmoset, a small new world primate, with a highly developed PFC, with similar cytoarchitectonic organisation to that of humans. Implanted cannulae were targeted at areas 25 and 32 of the marmoset mPFC, to enable temporary pharmacological inactivation by infusion of 0.5µl 0.1mM muscimol/1.0mMbaclofen (a GABAA and GABAB receptor agonist, respectively) in saline, or 0.5µl saline as a control. The effects of these manipulations on both cardiovascular and behavioural activity (as indices of emotion), were assessed under (i) an affectively neutral condition and (ii) following induction of a conditioned emotional response in an aversive Pavlovian discriminative conditioning paradigm. Under affectively neutral conditions, manipulations of areas 25 and 32 produced differential effects, with inactivation of area 25 reducing cardiovascular activity (heart-rate, heart-rate variability and sympathetic activity p< 0.05, 2-tailed t-test against saline) and vigilant scanning behaviour, whilst inactivation of area 32 increased vigilant scanning behaviour (p< 0.05, 2-tailed t-test against saline). Inactivation of both areas also disrupted behavioural and heart rate conditioned discrimination responses (during the aversive discrimination), although initial results suggest that this loss of discrimination is due to different effects of inactivation of area 25 versus area 32. The results suggest that temporary inactivation of areas 25 and 32 of the marmoset mPFC differentially effect behavioural and cardiovascular indices of emotion, with inactivation of area 25 producing an anxiolytic-like effect whilst inactivation of area 32 produces an anxiogenic-like effect. This study was supported by an MRC career development award to HC. CW is supported by an MRC BCNI studentship.
TC32

STRAIN RELATED DIFFERENCES IN BEHAVIOUR AND NEUROIMAGING MARKERS IN THE WISTAR AND WISTAR KYOTO RAT ARE ASSOCIATED WITH ALTERED ASTROGLIAL CELL NUMBER

Gormley S. School of Pharmacy and Pharmaceutical Sciences, Room 3.09, TCIN, Lloyd Bldg, Trinity College Dublin, College Green, D2, sgormley@tcd.ie
Kerskens C(1), Harkin A(1,2) (1) Trinity College Inst of Neuroscience, Trinity College Dublin. (2) School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin

The inbred Wistar–Kyoto (WKY) rat is a putative animal model of depression and hyper-responsiveness to stress and has previously been shown to exhibit a decrease in immunoreactivity for the astrocyte cell marker glial fibrillary acidic protein (GFAP) in specific brain regions. A growing body of clinical and pre-clinical evidence indicates reduced glial cell number/function in major depressive disorder. We sought to investigate if the WKY rat strain exhibited anatomical volumetric abnormalities and/or changes to cerebral blood perfusion in cortical and limbic regions of the brain as measured by magnetic resonance imaging (MRI) which may be associated with astroglial GFAP immunoreactivity ex vivo. Male Wistar (WIS) and WKY rats (200-250g, n=9) were subjected to a series of behavioural tests including exploratory behaviour in the open field (OF), behavioural despair in the forced swim test (FST) and anxiety-related behaviour in the elevated plus maze (EPM) to establish the behavioural phenotype. In preparation for MRI, animals were anaesthetised using 5% isoflurane (maintained at 1.5%) and placed into a 7-Tesla MRI scanner (Bruker BioSpec 70/30 magnet system). Structural data was obtained via a high resolution anatomical scan (T2-weighted Rapid Acquisition with Relaxation Enhancement (RARE)) and analysed by manual tracing of regions of interest. Blood perfusion was assessed via a bolus-tracking arterial spin labelling sequence (bt-ASL). 24 hours following the MRI scan animals were trans-cardially perfused with 4% paraformaldehyde and sections prepared for free floating GFAP immunofluorescence. The WKY strain exhibits a depressive/anxiety like phenotype across the range of behavioural paradigms including the OF, FST and EPM relative to the WIS control strain. The WKY strain exhibits volumetric abnormalities including a significant decrease in hippocampal volume (p<0.001) and an increase in lateral and third ventricular volume (p<0.001) relative to the WIS control strain. The WKY strain exhibits an increase in mean transit time (MTT) (p<0.05) and capillary transit time (CTT) (p<0.05) with a corresponding decrease in signal amplitude in the prelimbic cortex, striatum and third ventricle indicating a decrease in perfusion relative to the WIS control strain. The WKY strain exhibits lower GFAP positive cell number in the pre-limbic cortex relative to the WIS control strain (p<0.05). A negative correlation was observed between GFAP immunoreactivity and the perfusion markers quantified in this region (p<0.05). These data indicate that the WKY strain may be a suitable model to investigate associations between astroglial dysfunction and the biological correlates of perfusion and structural MR imaging markers of relevance to anxiety/depression related disorders. This research was funded by the School of Pharmacy and Pharmaceutical sciences, Trinity College Dublin.

TC33

IMMUNOMODULATORY PROPERTIES OF MONOAMINERGIC ANTIDEPRESSANTS AND OMEGA-3 POLYUNSATURATED FATTY ACIDS

Horowitz MA, Psych Med, KCL, CCBB, 125 Coldharbour Lane, London, SE5 9NU, mark.horowitz@kcl.ac.uk
Anacker CA(2), Wertz J(1), Zhu D(1), Pariante CM(1), Zunszain PA(1) (1) SPI Lab, KCL, London SE5 9NU (2) Meaney Lab, McGill, Montreal, Canada H4H 1R3

Introduction: There has been considerable interest in the immunomodulatory properties of antidepressant compounds because of the importance attributed to neuro-inflammation in the pathogenesis of depression. In particular, immunomodulation has been proposed as a common pathway of action for both monoaminergic antidepressants and omega-3 polynsaturated fatty acids (n-3 PUFAs). Their immunomodulatory effects have been described in peripheral human blood samples and animal brains, but are unknown in human brain cells. Here we investigate these properties in human hippocampal progenitor cells including an examination of a proposed underlying mechanism of NF-kB modulation, a key transcription factor in the inflammatory cascade. Methods: Human hippocampal progenitor cells (HPC03A/07) were co-incubated with the pro-inflammatory cytokine IL-1β and each of four monoaminergic antidepressants from different chemical classes – venlafaxine, sertraline, moclobemide and agomelatine - at two doses (100nM and 1uM) and two key n-3 PUFAs – docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) at two doses (1uM and 10uM). After 24 hours of incubation we measured cytokines and chemokines in the supernatant by ELISA and multiplex immunoassays, analysed gene expression by qPCR and determined NF-kB activity by a TransAM assay. In each experiment at least five repeats were conducted on at least five independent cell cultures. Results: We found that venlafaxine (1uM) was anti-inflammatory, causing decreased IL-6 secretion (-14% +/-5% [mean +/-SEM], p<0.001, n=8), associated with decreased NF-kB activity (-22% +/-8%, p<0.05, n=15). Unexpectedly, we found that sertraline (1uM) was pro-inflammatory, showing increased IL-6 (+27% +/-10%, p<0.001, n=8) and IFN alpha (+19% +/-7%, p<0.05, n=7), while decreasing NF-kB activity (-12% +/-3%, p<0.001, n=6). Agomelatine and moclobemide had no effect on IL-6 secretion. EPA (10uM) decreased inflammation broadly, reflected in levels of IL-6, IL-15, IL-1RA and IP-10, and decreased IL-6 mRNA and NF-kB activity (-15% +/-4%, p<0.001, n=9). DHA (10uM) had the opposite effect, increasing the inflammatory milieu, reflected in increased levels of IL-6, IL-15, IL-1RA, IFN-alpha, although this was associated with decreased NF-kB activity (-38% +/-11%, p<0.001, n=6). Conclusions: Here we have shown that monoaminergic antidepressants and n-3 PUFAs have differential effects on immune processes in human neural cells, showing more divergent actions than in peripheral blood or animal samples. Further research is needed to understand the exact mechanisms underlying these differential effects, including NF-kB dependent and –independent pathways. Increased understanding of these mechanisms may allow for improved targeting of key molecules for antidepressant effect. MH is funded by a King’s Overseas Research Studentship. This work was funded by a NARSAD Young Investigator Award to PZ and financially supported by the National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King’s College London.
TC34

KETAMINE INDUCES BIPHASIC CHANGES IN INTER-REGIONAL OXYGEN FUNCTIONAL CONNECTIVITY OVER 24H IN THE FREELY-MOVING RAT – AN ANTIDEPRESSANT BIOMARKER?

Li J, In Vivo Pharmacology, Eli Lilly & Co, Centre for Cognitive Neuroscience, Erl Wood Manor, Windlesham, Surrey UK, GU20 6PH, lije@lilly.com

In vivo oxygen amperometry is an alternative approach to functional magnetic resonance imaging that measures real-time extracellular tissue oxygen changes in freely-moving animals. Recently, imaging studies have begun focusing on intrinsic brain activity rather than evoked activity, exploring functional connectivity of different brain regions using low frequency BOLD correlations. Several abnormalities have been identified in resting-state connectivity in numerous neuropsychiatric diseases using this method, leading us to investigate similar properties in the oxygen amperometry signal using pharmacological manipulations. This study assessed the pharmacological modulation of the amperometric functional connectivity signal following administration of NMDA antagonist ketamine, a compound that has shown fast-acting antidepressant activity in human depressed patients. For in vivo oxygen amperometry studies, rats were implanted with carbon paste electrodes in four different brain regions; the prelimbic prefrontal cortex (PRL) infralimbic prefrontal cortex (IL), the amygdala (AMYG) and the retrosplenial cortex (RSC). Implanted rats were then dosed with either vehicle, or 10mg/kg S(+)-ketamine s.c in a within-subjects, cross-over design and signals recorded for 25h. The oxygen analysis, based on pharmacological fMRI and resting state fMRI methodologies, assessed the regional response up to 2 hours following ketamine administration, and the AUC was calculated as the magnitude of the response. For the functional connectivity analysis, linear correlations of oxygen signal slow fluctuations (0.01-0.1Hz) were performed in sliding windows and multiple frequency bins to build a correlation spectrum over time. Correlation data was binned into 2h time blocks and the key effects were summarized in the 2h and 22h response. Broadband correlation values were Fisher transformed and values were analysed by a Repeated Measures ANOVA followed by Fisher’s LSD post-hoc test for multiple comparisons. Our results show that the amygdala functional connectivity oxygen signal is modulated both acutely (2h) and on a longer timescale (22h) following ketamine administration, while other pairs of regions showed no significant changes in functional connectivity. There was a robust decrease in amygdala connectivity between 0-2h (PRLxAMYG p=0.003, ILxAMYG p<0.0001, RSCxAMYG p<0.0001), and a more subtle increase in amygdala connectivity 20-25h following ketamine (PRLxAMYG p<0.001, ILxAMYG p<0.001, RSCxAMYG p=0.05). At present, we believe in vivo oxygen amperometry is a valid translational surrogate for imaging studies in freely-moving animals, and measures of oxygen resting-state functional connectivity in rodents might predict human rsfMRI outcomes. The amygdala functional connectivity changes induced by ketamine may indicate a biomarker for its fast-acting antidepressant activity, which can be explored further in human imaging studies. Sources of financial sponsorship: All authors are employees of Eli Lilly & Co

TC35

REGIONAL SPECIFIC MODULATION OF NEURONAL ACTIVATION ASSOCIATED WITH THE ANTIDEPRESSANT-LIKE PROPERTIES OF NITRIC OXIDE SYNTHASE INHIBITORS

Sherwin E, Physiology, School of Medicine, Trinity College Dublin, Inst of Neuroscience, Room 3.09 Lloyd Bldg, Trinity College Dublin, Dublin 2, Ireland, Dublin 2, sherwie@tcd.ie

Gigliucci V (2,3) Harkin A (2,3) (2) School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin (3) Trinity College Inst of Neuroscience, Trinity College Dublin

Nitric Oxide Synthase (NOS) inhibitors display antidepressant and anxiolytic-like properties in several preclinical behavioural tests. There are numerous reports of antidepressant-like activity in the Forced Swimming Test (FST) and studies indicate that these behavioural effects are mediated through actions on the serotonergic system. The FST is a stressor, which induces robust neuronal activation in several brain regions associated with stress coping and depressive behaviour (immobility time), which is thought to reflect a behavioural state of despair. A combination of central serotonin-depletion with stress coping and depressive behaviour (immobility time), which is thought to reflect a behavioural state of despair. A combination of central serotonin-depletion with stress coping and depressive behaviour (immobility time), which is thought to reflect a behavioural state of despair. A combination of central serotonin-depletion. Male Sprague-Dawley rats (N= 5-6 per group) were treated once daily for three consecutive days with the irreversible tryptophan hydroxylase inhibitor, DL-4-p-chlorophenylalanine (pCPA, 150 mg/kg, i.p.), to achieve central serotonin-depletion. Animals were exposed to restraint stress for 2 hours per day for three consecutive days and were then subjected to the FST. 24, 5 and 1 hour prior to the test, animals were treated with either L-NA (10 mg/kg, i.p.), TRIM (50 mg/kg, i.p.) or saline vehicle (i.p). Both NOS inhibitors decreased immobility time (p<0.05) in keeping with their antidepressant-like properties. Brain regions analyzed included the prelimbic cortex (PLx), lateral septum (LS), nucleus accumbens (NAc), paraventricular hypothalamic nucleus (PNV), central amygdala (CeA), hippocampus (dorsal and ventral regions), and the dorsal raphe nucleus (DRN). The main observations were as follows: Exposure to the FST increased c-FOS immunoreactivity (p<0.01) in several of the brain regions assessed including the PLX, LS, PNV, dentate gyrus, vCA1 and the DRN when compared to non-FST exposed controls. FST-induced c-FOS immunoreactivity was further increased in the LS following treatment with L-NA or TRIM (p<0.01) when compared to vehicle-treated FST controls. By contrast, FST-induced c-FOS immunoreactivity was reduced in dDG, vCA1 and the DRN following treatment with L-NA or TRIM (p<0.01) when compared to vehicle-treated FST controls. In conclusion, a pattern of enhanced and reduced FST-related c-FOS immunoreactivity suggestive of a NO-regulated network where inhibition of NO leads to activation of the septum with concomitant inhibition of the hippocampus, and the DRN. Such a pattern of regulation by NOS inhibitors may relate to their antidepressant-like behavioural properties. This research is being funded by Trinity College Dublin
TC36

ACUTE AND CHRONIC LIPOPOLYSACCHARIDE INDUCES SICKNESS BUT FAILS TO PRODUCE A DEPRESSIVE-LIKE BEHAVIOUR IN MICE

Wickens RA, Pharmacy & Pharmacology, Univ of Bath, Claverton Down, Bath, BA2 7AY, raw36@bath.ac.uk

Ver Donck L(2), Mackenzie AB(1), Bailey SJ(1) (1) Dept. of Pharmacy & Pharmacology, Univ of Bath, Claverton Down, Bath BA2 7AY (2) Dept. of Neuroscience, Janssen Research & Development, A Div of Janssen Pharmaceutica NV, Beerse, Belgium 2340

Clinical evidence has implicated inflammation in the pathology of depression (Dantzer et al. 2008. Nat Rev. 9(1), 46-57). Acute administration of lipopolysaccharide (LPS) has been used to assess the role of inflammation in depressive-like behaviours in mice, though acute LPS induces transient inflammation and does not address the chronic nature of depression. Chronic LPS may model the sustained neuroinflammation thought to be present in depression (Kubera et al. 2013. Brain Behav Immun. 31, 96-104). Male C57BL/6J mice (10-14 weeks) were intraperitoneally injected with LPS (0.83 mg/kg) or saline every day for 3 or 5 days before being tested in the open field test (OFT) at +6 hours and the forced swim test (FST) at +24 hours after the final injection to assess sickness and depressive-like behavior, respectively. Behaviours were analyzed using an automated video-analysis system (Ethovision). Groups included acute LPS (administered only on day 3 or 5), chronic LPS constant dose (CD), chronic LPS increasing dose (ID; ending at 0.83 mg/kg) and a saline control. One-way ANOVA revealed a significant main effect of treatment in the OFT after 5 days (F(5,83)=20.58, P<0.0001) or 3 days (F(5,78)=45.56, P<0.0001). All LPS treatments induced a significant reduction in the distance travelled in the OFT compared to saline-treated controls (P<0.001 for all), along with a significant reduction in body weight (P<0.0001 for all). However, the reduced locomotion in the OFT was attenuated in 5 day chronic LPS CD and ID groups compared to acute LPS (P<0.001 & P<0.01, respectively). Interestingly, after 3 days chronic dosing, only the reduction in the CD (not ID) chronic LPS was significantly attenuated compared to acute LPS (P<0.001). However, no main effect of treatment in the FST was seen after 5 days (F(5,79)=1.275, P=0.2833) or 3 days (F(5,78)=1.162, P=0.3535). Acute LPS induced a strong sickness behaviour at +6 hours that was attenuated by chronic LPS administration, suggesting the development of tolerance. Previous reports have shown attenuated hypolocomotion following repeated LPS (Engeland et al. 2001. Physiol Behav. 72, 481-491). Interestingly, 3-day ID chronic LPS did not attenuate sickness behaviour, suggesting such treatment may circumvent the development of tolerance. However, no group exhibited a depressive-like behavior in the FST, suggesting that both acute LPS and chronic LPS (constant or increasing dose) do not provide a reliable neuroinflammation-based model for depressive-like behaviour. Support by MRC CASE PhD studentship with Janssen Research and Development, a Division of Janssen Pharmaceutica NV

TC37

AN INFLAMMATORY INSULT DURING THE PERINATAL PERIOD DIFFERENTIALLY ALTERS IMMUNE FUNCTION IN EARLY AND LATER LIFE: INSIGHTS FROM AN ANIMAL MODEL

Du Preez A, Dept of Psychological Medicine, Inst of Psychiatry, King’s College London, The James Black Centre, 125 Coldharbour Lane, London, SE5 9NU, andrea.du_preez@kcl.ac.uk

Gottlieb E(1), Musaelyan K(1), Thuret S(1), Fernandes C(2), Zunszain P(1), Pariante CM(1) (1) Dept. of Psychological Medicine, Inst of Psychiatry, King’s College London, The James Black Centre, 125 Coldharbour Lane, London, SE5 9NU. (2) MRC Social, Genetic & Developmental Psychiatry Centre, Inst of Psychiatry, King’s College London, De Crespigny Park, London, SE5 8AF.

Introduction: Exposure to an inflammatory insult in the perinatal period can increase susceptibility to further stress, permanently alter some aspects of the immune system and even predispose, or “sensitize”, individuals to a range of cognitive and neuropsychiatric disorders (Spencer et al., 2011 Am J Physiol Endocrinol Metab 300, E11-18). However, no study to date has examined the effect of perinatal immune challenge on immune function in both early and later life. Methods: Forty female BALB/cAnCrl mice received intraperitoneal injections of lipopolysaccharide (LPS), a bacterial endotoxin, at a dose of 0.33mg/kg on both postnatal day (P) 3 and P5, representing our “sensitized” animals. An identical number of “healthy” controls were injected with saline neonatally. P3/P5 approximately equates to the third trimester of pregnancy in humans (Gottlieb et al., 1977 Biol Neonate 32, 166-176). Using a cytokine mouse 10-plex LumineX assay, immunological changes in circulation were assessed when control and “sensitized” mice reached P14 and P45. Results: Compared with controls, “sensitized” mice exhibit significantly higher plasma levels of IL-6 in response to early life LPS challenge (M= 29.0 v 26.5; t (14) = -2.19, p = .046). In contrast, there was a trend for an attenuated immunological response to later life LPS challenge in “sensitized” animals compared with controls. Specifically, P45 “sensitized” mice show a trend for reduced levels of tumour necrosis factor (TNF)-alpha (M= 9.77 v 14.63; t(10) = 1.99, p = .069), interleukin (IL)-12 (M= 94.81 v 122.14; t(10) 2.19, p = .054), interferon (IFN)-gamma (M= 196.34 v 258.62; t (10) 2.19, p = .053) and granulocyte-macrophage colony-stimulating factor (GM-CSF) (M= 236.60 v 304.79; t (10) 2.19, p = .054) when compared with controls. Conclusion: Our data show how neonatal exposure to an inflammatory insult can differentially alter immune function in early and later life. An immune challenge during the perinatal period results in long-lasting alterations in the innate immune response to subsequent inflammatory insults. Funding This study was funded by Marie Curie actions FP7 and Janssen Pharmaceuticals.
MODULATION OF OXIDATIVE STRESS IN HUMAN HIPPOCAMPAL PROGENITOR CELLS: A MODEL TO STUDY UNDERLYING MECHANISMS OF DEPRESSION

Bakunina N., Psychological Medicine, King’s College London, The James Black Centre, Room 2-059, 125 Coldharbour Lane, London, SE5 9NU, nataliia.bakunina@kcl.ac.uk
Horowitz M(1), Pariante CM(1), Zunszain PA (1) Dept of Psychological Medicine, King’s College London, The James Black Centre, Room 2-059, 125 Coldharbour Lane, SE5 9NU London

Recent findings suggest that oxidative stress (OS) has an important role in the pathophysiology of depression. (Maes et al., Progress in Neuro-Psychopharmacology and Biological Psychiatry, 2011) OS is a pathological condition arising when the physiological oxidative actions by reactive oxygen species (ROS) are no longer balanced by antioxidative defenses. As ROS alter cells cytoarchitecture and function by damaging DNA, proteins and lipids, the presence of excess ROS in the brain could contribute to lower neuroplasticity and reduced neurogenesis, both of which have been linked to lower mood. A crucial challenge is therefore to delineate the molecular mechanisms underlying these associations, which would provide new potential targets to design more effective antidepressants. The multipotent, human hippocampal progenitor cell line, HPC03A/07 (provided by ReNeuron Ltd., Surrey, UK), was used for all experiments. Cells were plated on 96-well plates at a density of 1.5 × 10^4 cells per well and cultured for 24 h. Then OS was induced by treatment with increasing doses of tert-butylhydroperoxide (T-BHP), from 1 μM to 100 μM for 24 h. Cell viability was assessed by the MTS assay CellTiter 96® AQueous One Solution Cell Proliferation Assay (Promega), a colorimetric method, recording absorbance at 492 nm. Levels of Cleaved Caspase-3 (CC3) were measured by immunostaining and quantified vs total number of cells whose nuclei were labeled with Hoescht. Images were analysed with CellInsight, a platform for automated, quantitative cell imaging. Three biological replicates with four technical replicates per each condition were conducted. At a concentration of 25 μM and 50 μM it caused a reduction of 35% and 71%, respectively, compared with control (ANOVA p<0.001). Doses of T-BHP of 100 μM caused almost total cell death. Evaluation of the apoptotic marker CC3 at the same concentrations of T-BHP showed no significant changes. Our results suggest that oxidative stress-mediated death of human hippocampal progenitor cells does not involve apoptosis, with data indicating that they undergo necrotic-like caspase independent cell death instead (Kroemer and Martin, Nature Medicine 2005). This finding provides a research platform for our further studies on identifying potential targets of inhibiting oxidative stress-induced cell damage and in this fashion brings us closer to the understanding of pathogenesis of depression. The research is funded by the NIHR Biomedical Research Center for Mental Health and the Medical Research Council UK.

DIFFERENTIAL EFFECT OF ANTIDEPRESSANTS AND OMEGA-3 POLYUNSATURATED FATTY ACIDS ON THE REDUCTION OF NEUROGENESIS CAUSED BY IL-1β

Tojo LM, CCBB, Inst of Psychiatry, King’s College London, James Black Centre, Denmark Hill, London UK, SE59NU, luis.tojo@kcl.ac.uk
Danhui, Z(1), Horowitz, M(1), Pariante, CM(1), Zunszain, PA(1) (1) Centre for the Cellular Basis of Behaviour, James Black Centre, Denmark Hill, London SE5 9NU

Depression is one of the leading causes of disability worldwide and involves very large and increasing costs in public health every year. Reduced neurogenesis and increased inflammation have both been found as potential mechanisms underlying the neuropathology of depression. In particular, IL-1β, a pro-inflammatory cytokine reported to be increased in depressed patients, has been shown to reduce neurogenesis in animal and human cellular models. Our research aims to look at ways in which the detrimental effects of IL-1β on neurogenesis can be reversed by different drugs. We used a conditionally immortalized human hippocampal stem cell line (HPC03A/07, ReNeuron, UK) as a model of “depression in a dish”. Cells were allowed to proliferate for 72 hours followed by 7 days of differentiation, in the presence of IL-1β (10 ng/mL) and either the SSRI sertraline (1μM), the SNRI venlafaxine (1μM), or the omega-3 polyunsaturated fatty acids eicosapentaenoic acid (EPA, 10 μM) or docosahexaenoic acid (DHA, 10 μM). To assess changes in neuronal differentiation cells were subjected to immunocytochemistry and evaluated using CellInsight™ NXT High Content Screening platform. Levels of mRNA were measured by real-time quantitative polymerase chain reaction, and results were calculated using GAPDH and β-actin as housekeeping genes. While no changes were observed for EPA or venlafaxine, sertraline and DHA showed reductions in the number of MAP2 positive neurones (ANOVA p<0.05); in particular, sertraline and DHA decreased the number of matured neurones MAP2 by 32% and 30%, respectively. A possible mechanism underlying the neurogenesis reductions by IL-1β could be through changes in the enzymes involved in the kynurenine pathway, which is activated by IL-1β, such as indolamine-2, 3-dioxygenase (IDO), kynurenine 3-monooxygenase (KMO) and kynureninase (KYNU). Co-incubation of cells with IL-1β and sertraline increased the mRNA levels of IDO by 19% (p < 0.05) and KYNU by 24% (p < 0.001), and reduced the level of mRNA of KMO by 30% (p < 0.01). IL-1β with DHA reduced the mRNA levels of IDO by 34% (p < 0.01), KMO by 27% (p < 0.01) and increased the mRNA levels of KYNU by 78% (p < 0.05), while IL-1β with EPA increased KMO mRNA levels by 22% (p < 0.05). IL-1β with venlafaxine showed no significant changes on levels of these enzymes. Our results show a differential effect of monoaminergic antidepressants and fatty acids on the reduction of neurogenesis caused by IL-1β, not explained by changes in levels of kynurenine enzymes. Our research is funded by the NIHR Biomedical Research Center for Mental Health, the Medical Research Council, and the European Commission.
Increasing evidence supports the importance of epigenetic disturbances in schizophrenia pathogenesis. One epigenetic process is that of DNA methylation; methylation of the long interspersed nuclear element-1 (LINE-1) provides a measure of whole-genome methylation. One of the enzymes involved in DNA methylation process is methylenetetrahydrofolate reductase (MTHFR); the gene for this enzyme contains a C677T polymorphism, resulting in reduced enzyme activity (Lochman et al., 2013, Neuro Endocrinol Lett, 34(8):792-7) and which has been associated with the extent of LINE-1 methylation in schizophrenia (Berghardt et al, 2012, Epigenomics. 2012;4(3):261-8). The 677T allele has also been associated with schizophrenia risk, and allele dose-dependent risk for negative symptoms and executive dysfunction (Gilbody et al., 2007, Am J Epidemiol.;165(1):1-13). Thus, the aim of this study was to examine global DNA methylation of the brain in schizophrenia and determine whether the MTHFR polymorphism contributed to this measure. DNA was extracted from frontal cortical and hippocampal brain tissue collected post mortem from schizophrenia and healthy control subjects and was used to determine LINE-1 methylation using bisulfite pyrosequencing. DNA was also genotyped for MTHFR 677C/T using TaqMan genotyping assay. ANOVA and T test were used for statistical analysis. We found a significant difference in LINE-1 methylation between schizophrenia and controls samples in frontal cortex (p =0.0020; n = 22 in each group) and hippocampus (p = 0.0053; n= 22 in control, n= 22 in schizophrenia), with greater methylation in the schizophrenia samples in each region. We found no significant association between LINE-1 methylation and MTHFR genotype in either sample. No confounding effects of age or sex were apparent. This study identifies a global DNA hypermethylation in the brain in schizophrenia that is consistent across brain regions. However, this appeared to be unrelated to the MTHFR polymorphism. Further studies are needed to determine whether the hypermethylation seen here is associated with the disease process or a consequence of chronic treatment with antipsychotic drugs. Financial Support: HF is supported by a fellowship from Cnpq.
behaviour of the first DAO knockout mouse. Our primary objective was to assess both spatial and non-spatial short-term memory performance, given a focus on long-term spatial memory in the aforementioned studies. Our secondary objective was to confirm the heightened anxiety phenotype observed in the Dao1G181R mouse. Methods: Spontaneous recognition memory and T-maze spontaneous alternation were tested in DAO-/- mice and wildtype littermate controls (129SvEv strain). Recognition memory performance was tested in three modalities: object, spatial and odour. Mice were also subjected to a battery of approach/avoidance anxiety tests, including the open field test, elevated plus maze, successive alleys, light/dark box, and novelty-suppressed feeding (hyponeophagia). Results: Relative to wildtypes, DAO-/- mice demonstrated improved spatial recognition memory performance \([F(1,19)=8.968; P=0.007]\), enhanced odour recognition memory performance \([F(1,19)=5.858; P=0.029]\), and increased T-maze alternation accuracy \([F(1,44)=4.244; P=0.045]\). DAO-/- mice also displayed elevated anxiety; they made fewer centre entries in the open field \([F(1,34)=4.765; P=0.036]\), fewer open arm entries in the elevated plus maze \([F(1,44)=5.101; P=0.029]\), and spent less time in zones 2-4 of the successive alleys \([F(1,20)=7.072; P=0.015]\). Finally, DAO-/- mice spent less time in the light in the light/dark box \([F(1,32)=4.469; P=0.042]\) and took longer to begin feeding in the hyponeophagia test \([F(1,20)=5.134; P=0.035]\). Conclusions: These findings add to a growing body of evidence – both clinical and preclinical – linking altered DAO function with a range of behavioural changes. To the best of our knowledge, this is the first demonstration of enhanced short-term memory performance in a genetic mouse model lacking DAO activity. Consistent with our results, D-serine increases T-maze spontaneous alternation accuracy in wildtype rodents, while D-serine and DAO inhibitors enhance object recognition memory performance. Such findings have led to suggestions that D-serine and/or DAO inhibitors could improve cognition in schizophrenia patients.

Acknowledgements: The DAO mice were a generous gift from Pfizer Inc. DP is funded by a University of Oxford Christopher Welch scholarship. Additional funding for this work was provided by the Wellcome Trust and MRC.

**TD04**

**SCHIZOPHRENIA-RELATED POSTSYNAPTIC DENSITY PROTEINS IN ASSOCIATIVE LEARNING**

**Clifton NE**, NIMHRI, Cardiff Univ, Hadyn Ellis Bldg, Maindy Rd, CF24 4HQ, cliftonne@cardiff.ac.uk

**Thomas K(1), Hall J(1) (1) NIMHRI, Cardiff Univ, Hadyn Ellis Bldg, Maindy Rd, CF24 4HQ**

Proteins within the postsynaptic density (PSD) are involved in mediating the intracellular signalling cascades that lead to synaptic plasticity. Alterations in PSD proteins could underpin abnormal synaptic plasticity demonstrated in neuropsychiatric disorders such as schizophrenia. Since PSD proteins Homer1a, Ania-3 and DLG2 are associated with increased risk of schizophrenia-like manifestations (Norton et al. 2003, Am J Med Genet B Neuropsychiatr Genet 120B:18-21; Spellmann et al. 2011, J Psychiatr Res 45:234-241; Kirov et al. 2012, Mol Psychiatry 17:142-153), we evaluated their involvement in memory consolidation following contextual fear conditioning, using in situ hybridization. Adult male Lister Hooded rats (250-275g) were placed in a conditioning box for 2 min, before receiving a foot shock (0.6 mA, 2 sec). After one further minute, rats were returned to their home cages. In recall experiments, rats were put back in the same context 24 hours later for 2 min (recall group) or 10 min (extinction). Brains were extracted at 30 min, 2 h, 4 h, 8 h or 24 h after testing and frozen on dry ice. 14 micron brain slices were cut and in situ hybridization was performed using radioactively labelled oligonucleotide probes specific to the mRNA of interest. mRNA expression was quantified from autoradiographs and comparisons were made using two-way analysis of variance. Fear-conditioned rats displayed a transient increase in Homer1a expression in CA1 of the hippocampus, peaking 4 h after conditioning at 150% naive control expression. Conversely, hippocampal expression of the related gene Ania-3 was unaffected, but cortical expression was doubled 2 h after conditioning. Furthermore, hippocampal and cortical Ania-3 expression was increased in animals that had undergone latent inhibition of conditioned fear. DLG2 expression was unchanged following fear conditioning, consistent with its predicted constitutive expression. Following the recall or extinction of fear memory, Homer1a expression was increased by 60% in hippocampal CA1, whereas no change was observed in Ania-3 expression. These results suggest distinct roles for Homer1a, Ania-3 and DLG2 in memory consolidation and support their involvement in synaptic plasticity mechanisms relevant to schizophrenia. This PhD is funded by the Wellcome Trust.

**TD05**

**THE ROLE OF VOLTAGE GATED CALCIUM CHANNELS IN ASSOCIATIVE LEARNING**

**Sykes LH**, NIMHRI, Cardiff Univ, Hadyn Ellis Bldg, Maindy Rd, Cardiff, CF24 4HQ, sykeshl@cardiff.ac.uk

**Thomas KL(1), Clifton N(1), Trent S(1), Hall J(1) (1) NIMHRI, HEB, Maindy Rd, Cardiff CF24 4HQ**

Introduction: Variation in the CACNA1C gene has been found to show genome-wide significant association with bipolar disorder, schizophrenia and other psychiatric illnesses (e.g. Smoller et al., 2013, Lancet, 9875: 1371-9). Other calcium channel subunits and downstream calcium signalling have also been implicated in the etiology of schizophrenia and related disorders. CACNA1C codes for an L-type voltage-gated calcium channel alpha-1 subunit, which defines the voltage sensitivity and pharmacological properties of the channel pore. Calcium influx through these channels and the subsequent down-stream calcium signalling are necessary for certain types of synaptic plasticity and learning. Associative memory deficits are distinctive negative symptoms of schizophrenia and hippocampal activation has been found to be influenced by identified risk variants of the disorder (Pohlack et al., 2011, Mol. Psychiatry, 16: 1072-3). The role of calcium channel signalling pathways in cognitive processes known to be affected in schizophrenia is not yet fully understood. By investigating the activity dependent expression profiles of these genes during learning and the effects of inhibiting these pathways, we aim to understand the possible molecular mechanisms that link the genetic risk with specific symptoms of psychiatric illnesses. Methods: Using in situ hybridisation, the present study characterises the basal expression profiles of CACNA1C, CACNB2, γPKC and αCaMKII in the hippocampus and pre-frontal cortex of the rodent and human brain. We further characterised activity-dependent regulation in rats following contextual fear conditioning, extinction and latent inhibition. To understand the role of the risk genes in learning behaviour we investigated the behavioural effects of inhibition of L-type calcium channels. Diltiazem was infused bilaterally into the hippocampus at different time points to establish the effects on different aspects of associative learning. Results: Our genes of interest show distinct expression profiles in the hippocampus
and pre-frontal cortex. There is evidence of learning-dependent regulation of expression, with different profiles observed between genes and regions of interest. Time-course data following conditioning shows distinct expression profiles compared to extinction learning and latent inhibition up to 24 hours following manipulation. Infusion of Diltiazem was found to have effects on consolidation and extinction related behaviour (F(1.72, 17.17)=6.83, P<0.008) while having no effects on the acquisition of initial learned associations or recall when compared to infusion of PBS (F(2.12, 12.71)=1.48 P=0.25). Conclusions: Calcium channel and related signalling genes play a role in associative and inhibitory learning. The disruption of these pathways may provide a molecular link between the identified genetic risk and associative learning deficits observed in schizophrenia and related psychiatric illnesses. Funding for this research is provided by the Wellcome Trust.

TD06

**DIVERGENT ACTIONS OF A KV3 POSITIVE MODULATOR ON GAMMA FREQUENCY OSCILLATIONS IN THE MAMMALIAN NEOCORTEX IN VITRO**

**Gillougley C,** Inst of Neuroscience, Newcastle Univ, Henry Wellcome Bldg, The Medical School, Framlington Place, Newcastle upon Tyne, NE2 4HH, mark.cunningham@ncl.ac.uk

Rentesi G(1), Alvaro GS(2), Large CH(2), LeBeau FE(1), Cunningham MO(1) 1. Inst of Neuroscience, The Medical School, Newcastle Univ, Newcastle upon Tyne, NE2 4HH, UK. 2. Autifony Therapeutics Ltd, Medicines Research Centre Via Fleming 4, 37135 Verona, Italy

Neocortical neuronal networks produce synchronized gamma frequency oscillations (30-80 Hz) that are critical for processing and integrating cognitive modalities. Experimental studies have demonstrated that, in the presence of an appropriate pharmacological drive, such neuronal network activity is orchestrated by inhibitory mechanisms, notably GABAA receptor mediated events. Within this context, perisomatic targeting fast-spiking parvalbumin-containing (PV+) interneurons are capable of sustaining action potential output in the gamma frequency range. PV+ interneurons entrain the population of neocortical pyramidal neurons via gamma frequency GABAA-mediated IPSPs. This synchronised synaptic activity manifests at a population level as a coherent gamma frequency oscillation recorded as a local field potential (LFP). Kv3-family potassium channels such as Kv3.1 are selectively expressed in PV+ interneurons in the neocortex. Kv3 channels allow fast-spiking PV+ interneurons to fire accurately at high frequencies to orchestrate the activity of neocortical networks. Such high rates of firing, with high temporal accuracy, are required for the generation of neocortical gamma rhythms. Previous studies in patients suffering from schizophrenia (Uhlhaas PJ et al., J Neurosci. 2006 26(31): 8168-75) and putative animals models (Cunningham MO et al., J Neurosci. 2006 26(10): 2767-76) of the condition demonstrate an inability of neocortical networks to generate coherent gamma frequency oscillations. In addition, post-mortem studies using cortical tissue obtained from patients with schizophrenia report reductions in PV and in the expression of Kv3.1 channels in the remaining PV+ interneurons. Given that pharmacological manipulation of PV+ interneurons is a tangible therapeutic target for schizophrenia, we have examined the effect of a novel class of agents that positively modulate Kv3 channels. Brain slices were obtained from adult (> PND60) male Wistar rats. Slices containing primary auditory neocortex were prepared as previously detailed (Cunningham MO et al., Proc Natl Acad Sci U S A. 2004 101(18): 7152-7). Using kainate (400 nM), persistent gamma frequency oscillations were recorded as LFPs using extracellular microelectrodes. Application of AUT9 (10μM) did not significantly alter the peak power (4.9 ± 3.9 μV2 v. 3.0 ± 1.7 μV2 P > 0.05, n=8) and area power (102.0 ± 50.0 v. 82.0 ± 40.0 μV2 ; P > 0.05, n=8) of persistent slow (30 - 50Hz) gamma activity in the auditory cortex. The peak frequency of slow gamma frequency oscillations was not altered (42.8±3.6 v. 40.5 ± 3.1 Hz). In contrast, fast (>60 Hz) gamma oscillations were significantly increased for both peak power (2.0 ± 0.2 μV2 v. 2.6 ± 0.3 μV2; P < 0.05, n=5) and area power (105.0 ± 20.0 v. 130 ± 10.0 μV2; P < 0.05, n=5). The peak frequency of fast gamma oscillations was not significantly altered (67.1 ± 3.3 v. 65.8 ± 5.5 Hz). Our results suggest that modulation of Kv3 channels by these novel compounds may have the potential to correct disruptions in neuronal synchronization in schizophrenic patients by preferentially augmenting fast (> 60 Hz) neocortical gamma frequency oscillations. Sources of financial sponsorship: the work is supported by TSB Biomedical Catalyst award and Autifony Therapeutics Ltd

TD07

**KV3 CHANNEL MODULATION ALLEVIATES COGNITIVE DYSFUNCTION AND NEGATIVE SYMPTOMS IN AN ANIMAL MODEL OF SCHIZOPHRENIA: FIRST IDENTIFICATION OF A POTENTIALLY DISEASE MODIFYING TARGET FOR SCHIZOPHRENIA**

**Leger M,** Manchester Pharmacy School, Univ of Manchester, Oxford Rd, Manchester, UK, M13 9PT, marianne.leger@manchester.ac.uk

Grayson B(1), Marsh S(1), Alvaro G(2), Large C(3), Harte M(1), Neill J(1) (1) Manchester Pharmacy School, Univ of Manchester, Manchester, M13 9PT, UK (2) Autifony Therapeutics Ltd, Verona, Italy (3) Autifony Therapeutics Ltd, Imperial College Incubator, Bessemer Bldg, Imperial College London, SW7 2AZ, UK

Introduction: Cognitive dysfunction, along with negative symptoms, remain a clinical unmet need in schizophrenia; leading to schizophrenia being dubbed as the “forgotten illness”. Development of improved medication is therefore of the utmost importance. The potassium voltage gated ion channel, Kv3, mainly located on Parvalbumin (PV) GABAergic interneurons, is closely involved in brain circuitry thought to be affected in schizophrenia. Novel Kv3 channel modulators may thus improve therapy of this currently inadequately treated illness. The aim of the current study was to explore the efficacy of AUT9, a novel and selective Kv3 channel modulator, to improve cognitive and social behaviour impairment in our validated animal model of schizophrenia, sub-chronic PCP treatment in rats. To better understand the neurobiological mechanisms underlying the PCP effects, the influence of PCP treatment on PV and Kv3 channels expression was assessed in both the prefrontal cortex and hippocampus.

Methods: Three batches of 60 adult female hooded-Lister rats received sub-chronic phencyclidine (PCP; 2 mg/kg) or vehicle i.p. twice daily for 7 days, followed by 7 days washout. Then PCP-treated rats received risperidone (0.1 mg/kg, i.p.) or AUT9 (10-60 mg/kg, i.p.) and were tested in the reversal learning (RL), novel object recognition (NOR) or social interaction (SI) paradigms. A separate batch of PCP and vehicle-treated rats were used to determine the effects of PCP on PV and Kv3 channel expression using immunohistochemistry. Results: Sub-chronic PCP produced a significant and selective deficit in the RL task (P<0.001), that was significantly attenuated by AUT9 at all doses tested (P<0.05-0.001) and by risperidone (P<0.01). Similarly, the recognition deficits induced by PCP in the NOR task were alleviated both by AUT9 at all doses (P<0.05-0.001)
and risperidone (P<0.05). In the SI task, AUT9 at all doses significantly attenuated the reduced sniffing behaviour (P<0.05-0.001) and the increase in avoiding behaviour (P<0.001) induced by PCP. Immunohistochemical experiments demonstrate a significant reduction in the density of PV and Kv3 channel-positive cells respectively in hippocampus (-20%, P<0.05) and prefrontal cortex (-57%, P<0.05). Conclusion: These data demonstrate the efficacy of a novel molecule, AUT9, in two cognitive domains and negative symptoms in the PCP model of cognitive and social behaviour deficits of relevance to schizophrenia. Efficacy of AUT9 was also consistent with the observed reduction in PV and Kv3 expression in PCP-treated rats. These data suggest that modulation of Kv3 channels on PV interneurons could be an important novel approach for the treatment of schizophrenia. Sources of financial sponsorship: the work is supported by TSB and Autifony Declaration of interest from: JCN has received expenses to attend conferences and fees for lecturing and consultancy work (including attending advisory boards) from the manufacturers of various antipsychotic drugs

TD08

KV3 CHANNEL MODULATION AND LOW DOSE ANTIPSYCHOTICS INDUCE POSITIVE BIAS IN THE RODENT AFFECTIVE BIAS TASK

Gurney M, Manchester Pharmacy School, Univ of Manchester, Stopford Bldg, Oxford Rd, Manchester, M13 9PT, megan.gurney@postgrad.manchester.ac.uk

Leger M(1), Harte M(1), Grayson B(1), Alvaro G(2), Large C(3), Neill J(1) 1 Manchester Pharmacy School, Univ of Manchester, Manchester, M13 9PT, UK 2 Autifony Therapeutics Ltd, Verona, Italy 3 Autifony Therapeutics Ltd, Imperial College Incubator, Bessemer Building, Imperial College London, SW7 2AZ, UK

Introduction: Negative symptoms remain a clinical unmet need in schizophrenia and have proved difficult to treat, partly due to the lack of an effective animal model. Here we test the novel behavioural approach as described by Stuart et al. (Neuropsychopharmacology, 2013, 1-11) for current and novel antipsychotic medication. The antipsychotics risperidone, haloperidol and AUT9, a novel and selective Kv3 channel modulator (see Leger et al. this meeting) were tested. The anxiogenic compound, FG7142, was used to provide a negative control. The aim of the current study was to explore the effect of antipsychotics on affective states and to explore an animal behavioural test for negative symptoms. Methods: 50 adult female hooded- Lister rats were trained to dig in bowls to receive a food reward prior to pairing. Each task followed a standard protocol of four pairing sessions followed by a choice test session on the fifth day. The rats were split into 5 cohorts of 10 each receiving a different drug pairing. Each pairing session consisted of individual trials in which the rat was required to choose between two bowls. Following the pairing sessions the rats were presented with the two previously rewarded bowls over 30 trials. Rats either received: vehicle i.p., risperidone (0.1mg/kg, i.p.), haloperidol (0.05mg/kg, i.p.), FG7142 (10mg/kg, i.p.) or AUT9 (30mg/kg, i.p.). Results The antipsychotics tested all produced a significant positive bias at recall (risperidone p=0.0098, haloperidol p=0.0009, AUT9 p=0.0003), whilst the anxiogenic, FG7142 produced a significant negative affective bias at recall (p=0.0003). Vehicle treated rats showed no affective bias at recall suggesting that the drugs were responsible for altering the affective states of the rats (p=0.49). Latencies to dig were also recorded to account for any non-specific behavioural effects, no significant increase in latencies for any of the drugs tested was observed. Conclusion: These data show that a positive affective state can be induced by low doses of antipsychotics, which could be beneficial to patients with negative symptoms. It also shows that the novel compound AUT9 is as effective in producing a positive affective state as low doses of currently available antipsychotics. This finding in combination with AUT9's efficacy to reverse social behaviour and cognitive deficits in the PCP model (Leger et al. this meeting) supports the validity of this mechanism as a novel treatment for schizophrenia. Sources of financial sponsorship: the work is supported by the University of Manchester and Autifony therapeutics Ltd Declaration of interest from: JCN has received expenses to attend conferences and fees for lecturing and consultancy work (including attending advisory boards) from the manufacturers of various antipsychotic drugs

TD09

METABOLIC ANALYSIS REVEALS ALTERED PURINE AND AMINO ACID METABOLISM IN THE SUBCHRONIC PHENCYCLIDINE MODEL OF SCHIZOPHRENIA

Dawson N, Div of Biomedical and Life Sciences, Lancaster Univ, Lancaster, LA1 4YQ, n.dawson1@lancaster.ac.uk

MacIntyre L(1), Morris BJ(2,3), Watson DG(1), Pratt JA(1,2) (1) Strathclyde Inst of Pharmacy and Biomedical Science, Univ of Strathclyde, Glasgow, G4 0RE; (2) Psychiatric Research Inst of Neuroscience in Glasgow (PsyRING), Univs of Glasgow and Strathclyde, Glasgow, G12 8QQ (3) Inst of Neuroscience and Psychology, College of Medical, Veterinary and Life Sciences, Univ of Glasgow, Glasgow, G12 8QQ

Introduction In rodents prolonged NMDA receptor hypofunction, through subchronic treatment with phencyclidine (PCP), induces deficits in cognition and brain metabolism that have relevance to schizophrenia (Dawson et al., 2012. Schizophrenia Bulletin 38: 457-474). The various mechanisms through which prolonged NMDA receptor hypofunction induces these alterations are not fully understood. Here, to gain a holistic insight, we analyse the brains from rats treated subchronically with PCP using a metabolomics approach. Methods Metabolomic analysis of whole brain homogenates from male Lister Hooded rats treated subchronically with PCP (2.58mg/kg, i.p., once daily for 5 days with brains harvested 72 hours after the final drug treatment, n=5) or vehicle (0.9% saline, i.p., n=5) were analysed using LC-MS metabolomic analysis as previously described (Xiao et al., 2011. BMC Systems Biology 5: 72). SIEVE software (Thermo-Fisher Scientific) was used to detect significant differences in metabolite levels between the treatment groups, with significance set at P<0.05. KEGG reference metabolic pathways were used to identify those pathways disrupted by PCP treatment. Results Both significant increases and decreases in a range of metabolites from different KEGG defined metabolic pathways were found in the brains of PCP-treated animals relative to controls. This included 9 metabolites (6 decreases, 3 increases) involved in purine metabolism, 5 metabolites (3 decreases, 2 increases) involved in arginine and proline metabolism, and 3 metabolites (all decreased) involved in cysteine and methionine metabolism. In terms of purine metabolism, while adenosine monophosphate levels were found to be significantly increased (p=0.036, ratio = 1.13) many of its downstream metabolites were significantly decreased (adenosine, p=0.021, ratio=0.90; inosine p=0.018, ratio=0.847, hypoxanthine p=0.037, ratio=0.895) in the brains of PCP-treated animals. Similarly, while guanosine monophosphate...
(p=0.005, ratio=1.118) levels were increased its downstream metabolites (guanosine p=0.014, ratio=0.741 and guanine p=0.012, ratio=0.758) were decreased in the brains of PCP-treated animals. In addition, the levels of several amino acids, including L-Arginine (p=0.021, ratio=0.764), L-Tryptophan (p=0.006, ratio=0.855), L-Methionine (p=0.020, ratio=0.88) and L-Tyrosine (p=0.038, ratio=0.813) were found to be significantly decreased in the brains of animals treated with PCP. Conclusions Through the application of metabolomics we have identified metabolic pathways disrupted by prolonged NMDA receptor hypofunction in the brain. The deficits in purine and amino acid metabolism following subchronic PCP treatment may contribute to the brain and cognitive dysfunction seen in this animal model and in schizophrenia. Thus these metabolic pathways represent potential therapeutic targets for the treatment of these symptoms in the disorder. Financial Support This work was funded by the Psychiatric Research Institute of Neuroscience in Glasgow (PsyRING) and LM is supported by a BBSRC-funded CASE studentship in collaboration with MSD.

TD10

EFFECT OF APOCYNIN ON DISRUPTIONS IN BEHAVIOUR AND BRAIN GABAERGIC NEURONS IN THE SUBCHRONIC PHENCYCLIDINE RAT MODEL OF SCHIZOPHRENIA

Jenkins TA. School of Medical Sciences, RMIT Univ, P.O. Box 71, Bundoora, Victoria, Australia, 3083, trisha.jenkins@rmit.edu.au
Nediyedath K School of Medical Sciences, RMIT Univ, Bundoora, Victoria, 3083, Australia

Introduction: A sub-chronic administration of phencyclidine to the rat brings about enduring pathophysiological and cognitive changes that resemble some features of schizophrenia. The present study aimed to determine if concurrent administration of apocynin, an inhibitor of NADPH oxidase activity, could attenuate the effect of phencyclidine on behaviour and parvalbumin-containing neurons in the prefrontal cortex and hippocampus. Methods: Male Lister-hooded adult rats were administered phencyclidine at a dose of 5 mg/kg i.p. bi-daily for 1 week, or vehicle. Half of the phencyclidine group was concurrently treated with apocynin (5 mg/kg via the drinking water, 7 days before, 7 days during and 7 days after phencyclidine administration), with final numbers being control n=14, phencyclidine n=8 and phencyclidine + apocynin n=7. Novel object recognition memory (3min trial, 1hr ITI, 3min test) and locomotor activity (basal and phencyclidine-stimulated, 3.2mg/kg) were assessed 1 week post-phencyclidine treatment. Rats were then sacrificed, and brains removed and sectioned. Regions of prefrontal cortex and hippocampus were processed for parvalbumin immunohistochemistry. Results: Deficits in phencyclidine behaviour did not appear to be affected by concurrent apocynin treatment. With the novel object recognition task, phencyclidine treatment produced an inability for rats to discriminate between novel and familiar objects. This was not reversed by pre-treatment with apocynin (CON p<0.01; PCP p=0.68; PCP+APO p=0.62). No difference in basal locomotor activity was observed between groups (F<1), nor after acute phencyclidine administration (F(2,26)=2.0, p=0.16). Post-phencyclidine analysis of brains demonstrated a reduction in number of parvalbumin-immunoreactive neurons after phencyclidine treatment in regions of the prefrontal cortex (infralimbic p<0.01; prelimbic p<0.01; cingulate p<0.05) and hippocampus (CA1 p<0.01; CA2/3 p<0.05; dentate gyrus p<0.01, compared to control). Concurrent treatment with apocynin protected against the phencyclidine-induced deficits in regions of the prefrontal cortex (infralimbic cortex p<0.05) and hippocampus (CA1, p<0.05), that is the phencyclidine + apocynin group was shown to be significantly different from phencyclidine. In all other regions analysed, the phencyclidine + apocynin group had parvalbumin-immunoreactive neuronal numbers not significantly different from control, suggesting that apocynin in part rescued these neurons from the phencyclidine treatment. These results confirm the importance of the sub-chronic phencyclidine rat in modelling the behavioural deficiencies and brain pathology observed in schizophrenia, and suggest that concurrent apocynin is neuroprotective in this model. This research was funded by an internal grant from RMIT University.

TD11

EFFECT OF PHENCYCLIDINE ON PERSEVERANCE AND LEARNED IRRELEVANCE IN A TOUCHSCREEN REVERSAL LEARNING TASK IN RATS

Rafter MD. School of Life Sciences, Univ of Nottingham, Medical School, Queen’s Medical Centre, Nottingham, NG7 2UH, mbxmr1@nottingham.ac.uk
Moran P(1), Fone KCF(2) (1) School of Psychology, University Park, Univ of Nottingham, Nottingham NG7 2RD. (2) School of Life Sciences, Medical School, Univ of Nottingham, Nottingham NG7 2UH.

Introduction: Numerous studies show that NMDA receptor antagonists, such as phencyclidine (PCP), impair cognitive flexibility but spare acquisition learning in rodents and primates. Reversal learning requires the re-evaluation of associations such that formerly positive stimuli are depreciated and formerly negative/neural stimuli are appreciated. These two processes may however be mediated by distinct neuronal circuits and may be important to distinguish the nature of reversal learning deficits in disorders including addiction, schizophrenia, obsessive-compulsive disorder (OCD) and depression (Fineberg et al, 2010, Neuropsychopharmacology, 35: 591-604). Evaluation of these processes separately could explain some false positive findings, such as the improvement in reversal learning deficits by atypical antipsychotics in animal models of schizophrenia (Elsworth et al, 2012, Neuropsychopharmacology, 62: 1442-52), despite their lack of clinical efficacy in schizophrenia (Leeson et al, 2009, Biol Psychiatry, 66: 586-93). Methods: Forty adult male Lister-hooded rats were trained on an appetitive two-stimulus touchscreen visual discrimination. After acquisition, rats were assigned either to a simple reversal test (where the S+ becomes the S- and vice versa, n=16), perseverance test (where the S+ becomes S- and a novel S+ is introduced, n=12), or learned irrelevance test (where the S- becomes S+ and a novel S- is introduced, n=12). Half of the animals in each test received 2.5mg/kg PCP i.p. and half received vehicle (saline), twenty minutes prior to task sessions. Results: In the simple reversal, PCP significantly increased sessions to criterion (χ² = 3.84, d.f. = 1, p < 0.05) and total number of errors made (t14 = 4.21, p < 0.001). Sessions to criterion (χ² = 4.09, d.f. = 1, p < 0.05) and total errors (t9 = 3.66, p < 0.01) were also increased in the perseverance test. There was no effect of PCP in the learned irrelevance test (Sessions to criterion: χ² = 0.22, d.f. = 1, p > 0.05; Errors: t10 = 0.90, p > 0.05). Conclusions: PCP impairs reversal learning by delaying the extinction of previously rewarded associations, without affecting extinction of previously non-rewarded associations. Future experiments will characterise the effect of 5-HT2 receptor antagonists and atypical antipsychotics in this task. MDR was funded by the University of Nottingham.
TD12

AUTOMATIC HOMECAGE MONITORING OF RODENT BEHAVIOUR: EFFECTS OF PHENCYCLIDINE IN SOCIAL GROUPS OF RATS

**Brett RR**, SIPBS, Univ of Strathclyde, Glasgow, G4 0RE, ros.brett@cantab.net

Allison B(2), Armstrong JD (2,3), Pratt JA (1) (1) SIPBS, Univ of Strathclyde, Glasgow G4 0RE (2) Actual Analytics, Appleton Tower, 11 Crichton St, Edinburgh EH8 9LE (3) School of Informatics, Univ of Edinburgh, Edinburgh, EH8 9AB

The results from the LPS sensitized animals will provide much greater insight for comparison with in vitro literature. Investigation funded by the Scottish Funding Council Innovation Voucher

**ABSTRACTS**

**TD13**

THE ROLE OF ANTI-PSYCHOTIC MEDICATION IN CORTICAL INFLAMMATION

**Bloomfield PS**, Neuroplasticity and Disease/Psychiatric Imaging, Imperial College London/MRC, Robert Steiner Unit/3009 CRB Hammersmith Hospital, Du Cane Rd, London, W12 0NN, p.bloomfield11@imperial.ac.uk

West LA(1), Howes OD(2), de Paola V(1) (1) 3009 CRB, Hammersmith Hospital, Du Cane Rd, London W12 0NN (2) Robert Steiner Unit, Hammersmith Hospital, Du Cane Rd, London W12 0NN

**Introduction:** Antipsychotic medication is prescribed to schizophrenic patients, as well as those suffering from disorders such as major depression. Neuroinflammation is thought to be a part of schizophrenia (Doorduin, J et al., (2009). Journal of Nuclear Medicine 50, 1801-1807.) however the specific influence of antipsychotic medication has not yet been determined. In vitro evidence, based on LPS (lipopolysaccharide) activated microglial cell preparations, suggest an anti-inflammatory role for antipsychotic medication (Seki, Y et al., (2013). Schizophrenia Research. 151, 1–3). Here we investigate the role of antipsychotic medication in rats to determine the in vivo consequences of the first generation antipsychotic haloperidol. Methods: Rats were given haloperidol (0.05 mg/kg) (n=12) or placebo (n=20) via subcutaneous drug pellets over a two-week time course. A second cohort of animals (placebo n=6, haloperidol n=6) were dosed with both LPS (1 mg/kg over 2 weeks, 4 doses) and haloperidol to determine whether antipsychotic administration would influence microglia morphology in a systemically primed immune system. Blood samples were taken for measurement of haloperidol delivery and cytokine analysis. Animals were transcardially perfused and brains were dissected for immunohistochemistry. Prior to embedding and sectioning, brains were weighed and volumes were assessed for global changes in density (Dorph-Petersen, K.-A et al., (2005). Neuropsychopharmacology 30, 1649-1661.). Cryosectioned tissue was stained using Iba-1 (microglial marker) and DAPI (nuclear marker), z-stacks were acquired using a confocal microscope with the following regions of interest; PFC (prefrontal cortex), ventral striatum and hippocampus. Cell density and morphology were analyzed using adapted matlab software and Cell Profiler. Statistical analysis was performed using SPSS software. Between group effects were determined using a t-test and regional microglial densities were assessed using an ANOVA. An alpha threshold of 0.05 was considered as statistically significant. Results Blood drug level analysis confirmed release of haloperidol pellets (haloperidol dosed animals, 0.23±0.12 ng/ml, placebo dosed animals, 0 ng/ml haloperidol). Cytokine profiles were assessed for the LPS dosed cohort, however haloperidol administration did not significantly alter levels of TNFα, IL-6, CCL2, IL-2 IL-1β or IL-13. Brain volume in haloperidol animals was reduced and brain density increased when compared with placebo (1.58cm³ (0.30)*, 1.91cm³ (0.30), 1.38 g/cm³ (0.35)*, 1.14 g/cm³ (0.12)) (*p<0.01, **p=0.005) body weight was conserved across groups. Conclusion: The volumetric alterations are of a magnitude similar to those seen in human patient cohorts. Image analysis is ongoing to determine the effects of haloperidol treatment on microglia density and activation. The results from the LPS sensitized animals will provide much greater insight for comparison with in vitro literature. Investigation funded by the Medical Research Council
TD14

CHRONIC ANTIPSYCHOTIC TREATMENT INDUCES NEUROINFLAMMATORY CHANGES IN RATS

Cotel MC, Psychosis Studies, Inst of Psychiatry, KCL, James Black Center 125 Coldharbour Lane, London, SE5 9NU, marie-caroline.cotel@kcl.ac.uk
Lenartowicz EM(1), Natesan S(2), Modo M(3), Cooper JD(1), Williams SCR(2), Vernon AC(1), Kapur S(2) (1) James Black Center, 125 Coldharbour Lane, London SE5 9NU (2) Inst of Psychiatry, De Crespigny Park, London SE5 8AF (3) McGowan Inst for Regenerative Medicine, 450 Technology Drive, Suite 300, Pittsburgh PA 15219-3110

Introduction: The role played by antipsychotic (AP) treatments in the emergence and evolution of morphological and structural brain changes in schizophrenic patients is a pivotal question to answer. Animal studies allow us to circumvent the variables and confounding factors associated with human data. Previous work demonstrated that chronic AP in rats induces significant reduction of frontal cortical volume without changes in neuronal or astrocytic numbers (Vernon et al. 2013, Biol Psychiatry, in press). Our present study investigates the microglia response to chronic AP administration, following results from PET studies reporting an increased neuroinflammation in the hippocampus and grey matter of schizophrenics (Doorduin et al. 2009, J Nucl Med 50:1801-7). Methods: Adult male Sprague-Dawley rats were fitted with osmotic minipumps that delivered clinically relevant doses of AP drugs, haloperidol, (2 mg/kg/day) or olanzapine, (10 mg/kg/day), or vehicle, (n=8 per group) for 8 weeks. The animals were terminally anesthetized and transcardially perfused with saline solution followed by 4% paraformaldehyde. The brains were cryoprotected and sliced into 40 μm-thick sections. Series of every twelfth section were immunostained for microglia and astrocytes using Iba1 and GFAP antibodies. Microglial cells were stereologically quantified and classified according to their morphology. The number of cells was normalised to the regional volume estimated with the Cavalieri method. Astrocytic activation was evaluated using image thresholding. We primarily focused our investigation on the hippocampus (HPC), based on literature. Results: Strikingly, amoeboid microglia was dramatically increased in both drug groups (+161%, in haloperidol-treated animals compared to the vehicle group, P<.001; +144%, in olanzapine-treated animals, P<.001). The density of Iba1-positive cells was significantly increased in the haloperidol group compared to vehicle (+57%, P<.001). Resting microglia density was not significantly altered despite a strong trend toward an antipsychotic drug-induced increase. Activated microglia was slightly but significantly decreased after olanzapine treatment (-23%, P<.05). The levels of GFAP expression were not affected. Conclusions: This study shows that chronic treatment with antipsychotic drugs at relevant doses and duration in rats has a significant impact on microglia density but not astrocytic population, consistent with previous findings (Vernon et al. 2013). Further work is needed to assess the consequences on synaptic function and brain remodelling, the persistence of neuroinflammation after drug withdrawal, or the potential of anti-inflammatory compounds as adjunct treatments. This study was generously supported by a strategic funding from the Medical Research Council (Grant ID: G0701748 [85253] and G1002198).

TD15

TOWARDS IN VIVO MEASUREMENT OF THE DOPAMINE TURNOVER IN THE RAT STRIATUM USING [18F]FDOPA PET

Kokkinou M, Imperial College London, Hammersmith Hospital, Du Cane Rd, London W12 0NN, UK, W12 0NN, michelle.kokkinou08@imperial.ac.uk

Kokkinou M(1), Romiti A,(2), Coello C, (2), Wells L, 2, Howes O (1, 3) (1) Psychiatric Imaging Group, Imperial College, Hammersmith Hospital, London. (2) Imanova Centre for Imaging Sciences, Hammersmith Hospital, London. (3) Inst of Psychiatry, King’s College London, London.

Introduction: Dopamine (DA) synthesis capacity is thought to be disrupted in a number of neuropsychiatric disorders and potentially provides a translational neuropsychological marker for preclinical models of these disorders (Demjaha et al., 2012, Am J Psychiatry, 169, 1203-10). In this pilot study we aimed to validate [18F]fluoro-3,4-dihydroxyphenyl-L-alanine ([18F]FDOPA) PET methodology in rodents to measure presynaptic dopaminergic function. Methods: Following an i.v bolus administration of 10.6±4MBq of [18F]FDOPA, six Sprague-Dawley rats underwent a dynamic PET:CT scan (180min, Siemens Inveon PET:CT). Prior to scanning, three rats received a combination of benserazide hydrochloride (10mg/kg i.p., 30min) and tolcapone (40mg/kg i.p., 90min), inhibitors of peripheral aromatic L-amino acid decarboxylase (AADC) and catechol-O-methyl transferase (COMT) respectively. Images were reconstructed (2D-FBP) and Regions of Interest (ROIs) drawn on summed frames at the level of the striatum (Str) and cerebellum (Cereb) to extract Time Activity Curves (TAC). The average Standardized Uptake Values (SUV) for [18F]FDOPA were calculated between 75min and 150min (Inveon Research Workplace software). At the end of the scan, subjects were terminated and the amount of radioactivity in Str and Cereb regions determined. Data from treated and untreated subjects were compared by independent t-tests with an alpha level of 0.05. Results: [18F]FDOPA uptake was significantly higher in the image-derived ROIs of treated rats compared with control rats (Right Str P<0.05; left Str P<0.05 and Cereb P<0.05). Furthermore, clear striatal uptake of [18F]FDOPA was observed in rats treated with peripheral AADC and COMT inhibitors (image derived SUV75-150min: 1.36±0.15 and 1.37±0.13 for the right and left Str respectively). Compared to cerebellum, the striatal tissue kinetics of treated rats initially showed irreversible uptake (≤80 min) with a slow reversible component seen at later scanning timepoints; this is consistent with the biology of trapping (irreversible) and dopamine turnover (reversible). The PET scan results were confirmed by the tissue derived SUVs. Conclusion: The results of this pilot data support the use of [18F]FDOPA PET preclinically to measure [18F]FDOPA uptake in the Str. This enables us to investigate the effect of preclinical models of neuropsychiatric disorders impacting on the dopaminergic system. Further kinetic analysis is ongoing. MRC
TE01

A PRELIMINARY INVESTIGATION OF ASSOCIATIONS BETWEEN PHYSICAL FITNESS, ATTENTIONAL CONTROL AND GENERALISED ANXIETY DISORDER (GAD)

Andrews H, Clinical Neurosciences, Mental Health, Univ of Southampton: Faculty of Medicine, Academic Centre, College Keep 4-12 Terminus Terrace, Southampton SO14 3DT, ha1g10@soton.ac.uk

Rochester J, Matthews B, Collier-Keywood J, Baldwin D, Hou R. All: Academic Centre College Keep 4-12 Terminus Terrace Southampton SO14 3DT

Introduction: GAD is a common, debilitating mental health condition characterised by persistent and excessive, non-specific worry. It is the most prevalent of anxiety disorders, affecting 8% (Davidson J, Feltner D et al, 2010, v.12) of patients in primary care.Whilst there is an abundance of literature highlighting the beneficial effects of exercise in the treatment of chronic depression, there is less evidence surrounding its use in anxiety and attentional processing. Current NICE guidelines recommend a combination of anti-depressant medication and cognitive behavioural therapy, both of which have their limitations. Methods: A cohort study comprised 35 patients diagnosed with GAD, and 35 healthy matched controls recruited from the community and Southampton General Hospital. All participants completed 3 computer tasks of 10 minutes each where attentional control was measured objectively using the Attention Network Task (ANT). Attentional bias and executive function were also recorded to fulfill the protocol for a wider study. A questionnaire recorded individuals’ socio-demographic status, exercise levels, and anxious state. Height, weight and BMI were recorded alongside pre and post task blood pressure (BP). In order to provide a fair representation of overall physical fitness, a ‘fitness scale’ was then calculated for each participant comprising of an aggregate scoring system including: Blood Pressure Hours of exercise/day Activity level BMI Results: A significant difference in fitness score was found between groups (n=35, median difference=3.95% CI (1, 5), p=0.01). No significant difference between groups on alerting and orienting (measured using ANT) were found, however executive function score was significantly different between groups (n=35, mean difference=37.66, 95% CI (12.2,63.1), p=0.004). A significant negative correlation was found between both anxiety and fitness (r=-0.26, p=0.03) and depression and fitness (r=-0.39, p=0.001). A correlation was also found between anxiety and executive function (r=-0.25, p=0.04) and fitness and executive function (r=-0.25, p=0.04). Conclusion: It is important to highlight the findings showing poor executive function in patients with GAD, in order for those treating this group to be aware of the implications it may have on such patient’s quality of life. Although at present an un-validated measure, the ‘fitness scale’ used in this study involves some of the key components of physical well-being accepted in the medical profession. Significant at the level of p<0.05 there is a clear negative correlation between anxiety and fitness. This provides further evidence in support of including exercise as a formal treatment for anxiety and the eventual revision of NICE guidelines.

TE02

BEHAVIOURAL AND VOLUMETRIC CORRELATES OF REFLECTION IMPULSIVITY IN BINGE DRINKING

Banca P, Psychiatry, Univ of Cambridge, Addenbrooke’s Hosp, Cambridge CB2 2QQ paula.banca@gmail.com


Introduction: The weighing and evaluation of evidence is intrinsic to all decisions. It can be a trivial cognitive process or it can require careful deliberation. The degree to which an individual accumulates evidence before making a decision can be affected in psychiatric disorders. Here we study decisional impulsivity in binge drinkers, a group at elevated risk for developing alcohol use disorders, comparing two tasks assessing reflection impulsivity and a delay discounting task, hypothesizing impairments in both subtypes of impulsivity. We also assess volumetric correlates of reflection impulsivity focusing on regions previously implicated in functional MRI studies. Methods: Sixty binge drinkers and healthy volunteers were tested using two different information-gathering paradigms aiming to assess the degree of evidence accumulated before committing to a decision: the Beads Task and the Information Sampling Task (IST). The Beads task was analyzed using a behavioural approach and a Bayesian model of decision-making. Delay discounting was assessed using the Monetary Choice Questionnaire. Regression analyses of primary outcomes were conducted with voxel based morphometry analyses. Results: Binge-drinkers sought less evidence prior to decision in the Beads task compared to healthy volunteers in both the behavioural and computational modeling analysis. This enhanced reflection impulsivity in the Beads task correlated with alcohol severity. Although there were no differences in the evidence accumulated using the IST, in response to an explicit cost to the evidence accumulated, binge drinkers improved the capacity to integrate information and increased the number of total points earned. There were no group differences in the Delay Discounting task. The Beads task and IST were associated with dissociable volumetric regions. Greater impulsivity or less evidence accumulated in the Beads task was associated with lower volumes of the left dorsolateral prefrontal cortex and left insula. In contrast, less evidence accumulated in the IST task was associated with lower bilateral ventral striatal volume. Conclusions: Binge drinking is characterized by impaired reflection impulsivity suggesting a deficit in deciding on the basis of future outcomes that are more difficult to represent. These findings emphasize the role of possible therapeutic interventions targeting decision making deficits. This work was supported by the Wellcome trust and the Portuguese Foundation for Science and Technology.
**TE03**

**OBSESSIVE COMPULSIVE DISORDER PATIENTS DEMONSTRATE INCREASED CERTAINTY SEEKING BEHAVIORS IN AN OPERANT OBSERVING RESPONSE TASK: A TRANSLATIONAL APPROACH**

*Morein-Zamir S*, Psychology, Univ of Cambridge, BCNI, Downing Site, CB2 3EB, sm658@cam.ac.uk

Shahper S(1), Fineberg NA(1), Eagle DM(2,3), Urcelay G(2,3), Mar AC(2,3), Sahakian BJ(1,2,4), Robbins TW(2,3) (1) Hertfordshire Partnership NHS Univ Foundation, Trust, QEI, Welwyn Garden City (2) Behavioural and Clinical Neuroscience Inst, Univ of Cambridge, Downing Site, CB2 3EB (3) Dept of Psychology, Univ of Cambridge, Downing Site, CB2 3EB (4) Dept of Psychology, Univ of Cambridge, Addenbrooke’s Hosp, Cambridge CB2 2QQ

Introduction: Obsessive Compulsive Disorder (OCD) has been linked to numerous cognitive theories, such as increased intolerance of uncertainty. Certainty seeking may be one process underlying excessive checking behavior. We sought to obtain objective and quantitative measurements of certainty seeking behaviors in patients in a translational task. A rodent version of the observing response task has previously demonstrated excessive checking under chronic quinpirole administration (Eagle et al., in press, Behav Brain Res). Methods: We tested 21 OCD medicated patients that did not have any comorbid disorders, and 21 age and gender matched controls on this novel operant paradigm. Here, participants pressed two buttons in order to earn rewards on two corresponding variable ratio schedules. At any one time, only one of the buttons is ‘active’ thereby leading to rewards. Importantly, participants can press a third, ‘observing’ button that always cues the currently active button. In the baseline condition pressing on the ‘inactive’ button resulted in no rewards being earned, in a subsequent condition, pressing on the ‘inactive’ button resulted in punishments being delivered on a variable ratio schedule. Results: Patients with OCD pressed the ‘observing’ button more than controls in the baseline condition (F(1, 40)=6.6, p<0.05) and avoided pressing the inactive button to a greater degree (F(1, 40)=8.8, p<0.01). When the inactive button pressing was punished, the patients did not differ in their observing responses but now healthy controls pressed the observing button significantly more, reaching the level of observing responses exhibited by the patients (interaction: F(1, 40)=5.4, p<0.05). Patients reported greater anxiety (F(1, 40)=4.2, p<0.05) during the task, but did not significantly differ on amounts of rewards or punishments obtained (p>0.5 for both comparisons). Conclusions: Greater certainty seeking was found in OCD patients, as captured by the increased observing button pressing during baseline. The results further indicated that in contrast to healthy controls, the patients were insensitive to any actual negative consequences of being uncertain. This study is consistent with the notion that increased intolerance of uncertainty could contribute to clinical symptomatology. Moreover, the results provide validation for this translational paradigm reinforcing the rodent version. This study was supported by a Wellcome Trust Programme Grant (089589/z/09/z; PI TW) and completed within the University of Cambridge Behavioural and Clinical Neuroscience Institute, supported by a joint award from the Medical Research Council and the Wellcome Trust.

**TE04**

**COGNITIVE FLEXIBILITY IN OCD: FINDINGS FROM A NOVEL REVERSAL LEARNING TASK**

*van der Flier FE*, Dept of Psychiatry, Univ of Cambridge, Herschel Smith Bldg, Robinson Way, Addenbrooke’s Hospital, Cambridge CB2 0SZ, fv246@medschl.cam.ac.uk

Apergis-Schoute AM (1,2), Vaghi MM (2,3), Kaser M (1), Robbins TW (2,3), Sahakian BJ (1,2) (1) Dept of Psychiatry, Univ of Cambridge, Herschel Smith Bldg, Robinson Way, Addenbrooke’s Hospital, Cambridge CB2 0SZ (2) Behavioural and Clinical Neuroscience Inst, Univ of Cambridge, Downing Site, Cambridge CB2 3EB (3) Dept of Psychology, Univ of Cambridge, Downing Site, Cambridge CB2 3EB

Obsessive-compulsive disorder (OCD) affects approximately 50 million people worldwide (Sasson et al., 1997) and is characterized by intrusive thoughts as well as repetitive behaviours (Franklin and Foa, 2011). Impaired cognitive flexibility and inhibitory processes are central to the neuropsychopathology of the disorder, as demonstrated by cognitive tests (Chamberlain et al., 2005) with widespread but somewhat inconsistent findings of deficits in memory, planning, decision making, set shifting and executive control (Kuelz et al., 2004). Although impaired cognitive flexibility appears central to OCD dysfunction, performance on reversal learning – a key task depending on flexible executive functioning – has been found to be unaffected in OCD patients. The absence of a behavioural deficit during probabilistic reversal learning in OCD is perhaps due to the relatively low cognitive and emotional load of the task, while everyday flexible responding is often required during stressful and demanding situations. We hope to address this issue with a novel reversal learning task which combines a high cognitive load with pressure through limited time, reward and punishment. Based on growing evidence from neuroimaging studies in patients with OCD, a model that emphasizes disturbed fronto-striatal systems has emerged (Menzies et al., 2008). Using probabilistic reversal learning, Chamberlain et al. (2008) found that OCD patients had reduced activation in the lateral orbitofrontal cortex compared to controls, in absence of behavioural deficits. We are using our novel reversal learning task alongside several CANTAB tests and questionnaires in order to gain insight into hypothesized differences in the flexibility of cognitive control between OCD patients and controls, while employing diffusion tensor imaging (DTI) to be able to look at correlates with possible white matter tract abnormalities. Preliminary results of our novel reversal learning task show a clear effect of reward on accuracy (F(1,9)=7.742, p<.05) and reaction time (F(1,9)=2.18.03, p<.01) in 10 control participants. Responding on rewarding trials is significantly more accurate than on neutral trials. Also, reaction times are significantly faster on reward compared to neutral or punishment trials, while reaction times on punishment trials are still significantly faster than on neutral trials (all p<0.01). We are hopeful that this modulation through punishment and reward on our demanding reversal learning task, which involves switching responses between hands, will further our understanding of reduced cognitive flexibility in OCD and its relation to altered white matter connectivity of fronto-striatal pathways.
**ABSTRACTS**

**TE05**

**HYPOACTIVATION AND HYPOCONNECTIVITY OF THE FRONTO-STRIATAL LOOP IN OBSESSIVE-COMPULSIVE DISORDER**

Garner M, Teeling J, Culliford D, Baldwin D

Hampshire A (1), Fineberg NA (2), Brühl AB (3,4), Sahakian BJ (3,4), Chamberlain SR (3,4), Robbins TW (4,5) (1)The Computational, Cognitive and Clinical Neuroimaging Lab, The Div of Brain Sciences, Imperial College London, London SW7 2AZ, UK. (2) Highly Specialized Obsessive Compulsive and Related Disorders Service, Hertfordshire Partnership NHS Univ Foundation Trust, Queen Elizabeth II Hospital, Welwyn Garden City AL7 4HQ, UK and Univ of Hertfordshire, College Lane, Hatfield, UK. (3) Dept. of Psychiatry, Univ. of Cambridge, Cambridge CB2 0QQ, UK. (4) Behavioural and Clinical Neuroscience Institute (BCNI), Univ. of Cambridge, Cambridge CB2 3EB, UK. (5) Dept. of Psychology, Univ. of Cambridge, Cambridge CB2 3EB, UK.

Obsessive-compulsive disorder (OCD) is a highly heritable neuropsychiatric disorder (Pauls, 1995, Am J Psychiatry, 152, 76-84). Endophenotype, intermediate markers of brain disorder, represent a promising approach to elucidate the neurobiology of OCD. Previous studies have demonstrated impaired planning capacity in OCD patients, which has been linked with hypoactivation of dorsal prefrontal-striatal circuitry (Van den Heuvel et al., 2005, Arch Gen Psychiatry, 62, 301-309). In the present study, we assessed brain activation during executive planning, as a possible neurocognitive endophenotype of OCD. Fourteen OCD patients, 13 first-degree relatives, and 13 matched comparison subjects performed the One Touch Spatial Planning task (Williams-Gray et al., 2007, J Neurosci, 27, 4832-4838; Hampshire et al., 2013, Sci. Rep., 3, 2972) during fMRI. Percentage of problems attempted that were answered correctly and mean response times were used to measure behavioural performance by means of repeated measures ANOVAs. EPI images were acquired with a 3T Siemens scanner. Imaging data were analysed with SPM8. General Linear Model statistical analysis was used and a two-stage random-effects approach was adopted (FWE, p<0.05). Functional connectivity was investigated by means of PPI in SPM8. There was no difference between groups in proficiency of task performance in terms of correct responses (F (2, 37)=0.328, p=0.723). Irrespective of difficulty level and type of task (counting, planning), there was a main effect of group on response times (F (2, 37)=3.805, p=0.031), with patients being significantly slower to respond than controls (p=0.037) as were relatives (p=0.014). During planning, OCD patients and relatives showed significant hypoactivation in the right dorsolateral prefrontal cortex (DLPFC) vs. controls. There were no significant differences between relatives and patients. Reduced functional connectivity was found in OCD patients between right DLPFC and putamen (pair-wise comparisons by non-parametric permutation testing two tailed, controls vs. patients, p=0.017; controls vs. relatives, p=0.085; patients vs. relatives, p=0.220) during planning. Behavioural data showed that OCD patients and relatives achieved the same number of correct responses compared to controls at the expense of longer response times. Reduced planning-related activity in the right DLPFC appears to be a candidate neurocognitive endophenotype of OCD. Hypoactivation of the right DLPFC might constitute the underlying neural substrate responsible for less efficient cognitive strategies in OCD patients. Impaired fron-to-striatal functional connectivity during planning might be related to the clinical manifestation of OCD and relate more generally to known deficits in goal directed behaviour (Gillan et al., Am. J. Psychiatry, 179, 15-21). Supported by a Wellcome Trust Programme Grant (076274/Z/04/Z) to T.W.R., B.J.S., B. J. Everitt, and A. C. Roberts.

**TE06**

**A PRELIMINARY INVESTIGATION OF ASSOCIATIONS BETWEEN ATTENTIONAL CONTROL AND NEUROINFLAMMATION**

Hou R, Dept of Psychiatry, Univ of Southampton, Academic Centre, College Keep 4-12 Terminus Terrace, Southampton SO14 3DT, r.hou@soton.ac.uk

Garner M, Teeling J, Culliford D, Baldwin D

Background: Research into psychoneuroimmunology has led to substantial advances in our understanding of the reciprocal interactions between the central nervous system and the immune system. Experimental and clinical research reveals the pivotal roles of cytokines signalling to the brain to produce neurochemical, neuroendocrine, neuroimmune, and behavioural changes. Aims: The aim of this study was to investigate associations between cognitive processing and neuroinflammatory changes, in particular associations between attentional control and peripheral cytokines. We hypothesized that certain neural cognitive processing may be associated with certain peripheral inflammatory changes. Methods: 51 healthy volunteers, aged 26.15 ± 9.64 (Mean ±SD), 26 males, BMI 22.57±3.31 (Mean ±SD), were recruited. The attention control scale (ACS) was used to measure the ability to focus and shift attention. Levels of anxiety and depression were measured using the Hospital Anxiety Depression Scale. Serum levels of cytokines including, IL-1, IL-2, IL-4, IL-5, IL-8, IL-10,IL-12p70, IL-13, TNF-α and IFN-γ , were measured using a multiplex immunoassay Meso Scale Discovery (MSD, Human Demonstration 10-Plex). Results: Correlation analysis revealed that IL-5 and IL-10 were significantly associated with anxiety (p=0.040 and p=0.049), IL-4 was significantly correlated with ANT-orienting (p=0.047) and ANT-executive control (p=0.038). IFN- γ was significantly correlated with ACS-attention shift (p=0.046).

Conclusion: This preliminary study provides research evidence for neuroinflammatory changes associated with neurocognitive processing, in particular attentional control. The study suggests that impaired attentional control may be associated with specific inflammatory marker. Further work from the larger sample is needed to verify these preliminary findings. The project is funded by the University of Southampton.

A PRELIMINARY INVESTIGATION OF ASSOCIATIONS BETWEEN ATTENTIONAL CONTROL AND NEUROINFLAMMATION

Hou R, Dept of Psychiatry, Univ of Southampton, Academic Centre, College Keep 4-12 Terminus Terrace, Southampton SO14 3DT, r.hou@soton.ac.uk

Garner M, Teeling J, Culliford D, Baldwin D

Background: Research into psychoneuroimmunology has led to substantial advances in our understanding of the reciprocal interactions between the central nervous system and the immune system. Experimental and clinical research reveals the pivotal roles of cytokines signalling to the brain to produce neurochemical, neuroendocrine, neuroimmune, and behavioural changes. Aims: The aim of this study was to investigate associations between cognitive processing and neuroinflammatory changes, in particular associations between attentional control and peripheral cytokines. We hypothesized that certain neural cognitive processing may be associated with certain peripheral inflammatory changes. Methods: 51 healthy volunteers, aged 26.15 ± 9.64 (Mean ±SD), 26 males, BMI 22.57±3.31 (Mean ±SD), were recruited. The attention control scale (ACS) was used to measure the ability to focus and shift attention. The attention network task (ANT) was used to measure attentional control, which includes alerting, orienting and executive control. Levels of anxiety and depression were measured using the Hospital Anxiety Depression Scale. Serum levels of cytokines including, IL-1, IL-2, IL-4, IL-5, IL-8, IL-10,IL-12p70, IL-13, TNF-α and IFN-γ , were measured using a multiplex immunoassay Meso Scale Discovery (MSD, Human Demonstration 10-Plex). Results: Correlation analysis revealed that IL-5 and IL-10 were significantly associated with anxiety (p=0.040 and p=0.049). IL-4 was significantly correlated with ANT-orienting (p=0.047) and ANT-executive control (p=0.038). IFN- γ was significantly correlated with ACS-attention shift (p=0.046).

Conclusion: This preliminary study provides research evidence for neuroinflammatory changes associated with neurocognitive processing, in particular attentional control. The study suggests that impaired attentional control may be associated with specific inflammatory marker. Further work from the larger sample is needed to verify these preliminary findings. The project is funded by the University of Southampton.
TE07

AN INVESTIGATION OF PERIPHERAL CYTOKINES IN RELATION TO ANXIETY AND DEPRESSION MEASURED BY THE HOSPITAL ANXIETY AND DEPRESSION SCALE

Rochester JJ, Academic Psychiatry, Faculty of Medicine, Univ of Southampton, College Keep, Terminus Terrace, Southampton, SO14 3DT, jr1g09@soton.ac.uk
Matthews B(1), Andrews H(1), Collier-Keywood J(1), Garner M(1), Baldwin D(1), Hou R(1). (1) Dept of Academic Psychiatry, Faculty of Medicine, College Keep, Terminus Terrace, Southampton, SO14 3DT

Cytokines act as neurological, endocrine and immune modulators and are key research targets in the field of psychoneuroimmunology. Multiple studies have established the immune dysregulation hypothesis of major depression. However, the high co-morbidity between anxious and depressive disorders necessitates further investigation of cytokines in anxiety, and how any immune changes found compare to those reported in depression. As anxious and depressive symptoms are experienced at sub-clinical levels this study looks at a healthy population sample. The Hospital Anxiety and Depression Scale (HADS) is an accessible, established measure for both self-reported anxiety and depression. It enables the two psychiatric entities to be studied separately and at the same time produce easily comparable results. This study aims to test the hypothesis that levels of peripheral cytokines vary in relation to HADS anxiety and depression scores in the healthy population. Also to investigate any differences in cytokine levels between high self-reported anxiety and depression groups. As part of a larger study, 52 healthy volunteers from the general public aged 18-65 years completed the HADS questionnaire and had a venous blood sample taken. Levels of IL-1, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, TNF-α and IFN-γ were measured in the serum using a multiplex immunoassay. Participants were designated into high and low anxiety and depression groups according to their HADS scores. Lower levels of IL-10 (p=0.029) were measured in the high anxiety group compared to the low anxiety group using a Mann-Whitney U test. A weak negative correlation was seen between anxiety scores and IL-5 (r=-0.30) and IL-10 (r=-0.30) calculated with Spearman’s test. A weak negative correlation was also seen between depression scores and IL-5 (r=-0.29) but no significant differences were observed in cytokine levels between the high and low depression groups. HADS anxiety and depression scores were strongly positively correlated (r=0.64). This study finds that cytokine levels differ in relation to HADS self-reported levels of anxiety in the healthy population. A comparable negative correlation with IL-5 is evidence of a similarity between anxiety and depression and may tentatively suggest an immune link in their pathophysiology. In contrast, lower levels of IL-10 associated with higher anxiety scores may represent an immune difference between anxiety and depression. The strong association between anxiety and depression scores conforms to documented high co-morbidity rates. Findings from this study could support explanatory models of neuropsychiatric disorders which integrate the neurological and immune systems.

TE08

INTERFERON-ALPHA INDUCED PERSISTENT FATIGUE: A PILOT STUDY EXAMINING PUTATIVE BIOLOGICAL MECHANISMS

Russell AE. Stress, Psychiatry & Immunology (SPI) Lab, Psychological Medicine, Kings College London, Inst of Psychiatry, James Black Centre, 125 Coldharbour Lane, SE5 9NU, alice.russell@kcl.ac.uk
Cattaneo A (1), Hepgul N (2), Borsini A (1), Zajkowska Z (1), Baumeister D (3), Zunszain PA (1), Pariante CM (1). (1) Dept of Psychological Medicine, Kings College London, Inst of Psychiatry, James Black Centre, 125 Coldharbour Lane, SE5 9NU (2) Health Service and Population Research, Kings College London, Inst of Psychiatry, David Goldberg Centre, De Crespigny Park, SE5 8AF (3) Dept of Psychology, Kings College London, Inst of Psychiatry, Henry Wellcome Bldg, De Crespigny Park, SE5 8AF

Interferon-alpha (IFN-α) used to treat Chronic Hepatitis C Viral (HCV) infection induces acute fatigue that can persist up to six months post-treatment. Little research has been conducted utilizing peripheral blood gene expression techniques to explore the pathogenesis of persistent fatigue. This study uses this method to examine some putative biological mechanisms underlying the development of such a side effect. We recruited 25 patients receiving IFN-α, using a prospective cohort design. Blood samples were collected using PAXgene Blood RNA Tubes at baseline and treatment weeks 4, 12 and 24. Gene expression microarray assays were performed using Affymetrix® Human Gene 1.1 ST Array strips, and pathway analyses run using Ingenuity Pathway Analysis software. Fatigue was assessed using the Chalder Fatigue Questionnaire (CFQ), administered at baseline and six months post-treatment. Patients were stratified according to whether their fatigue levels at follow-up had improved or returned to baseline levels (Resolved Fatigue; RF, n = 15) or worsened (Persistent Fatigue; PF, n = 10). At baseline, we identified 52 putative predictor genes of persistent fatigue, differentially expressed in RF versus PF groups. Interestingly, among these genes we found CLEC4C (fold-change +1.52, p<0.002), associated with systemic lupus erythematosus (SLE), an auto-immune condition characterised by debilitating fatigue. NRG1, previously linked to dysregulation of the circadian rhythm and subsequent fatigue in cancer patients, also featured (+1.46, p=0.005). Assessing the effect of IFN-α, we found that at week 4, 663 genes were differentially expressed in both groups, compared to baseline. 229 were uniquely modulated in the RF group, and 556 in the PF group. Pathway analysis showed that among others, IL-15 and Tec Kinase signaling pathways were significantly altered in the PF group only. Molecules of interest within those pathways included BCL2 (+1.50, p<0.005), STAT1 (+1.57, p<0.0002) and FCER1A (-2.0, p<0.0002), all previously shown to be relevant to the immune system and fatigue. Our data shows a differential modulation of inflammatory pathways by IFN-α in patients that develop persistent fatigue, suggesting a possible underlying role in the development of related symptoms. Acknowledgments: This work was supported by the Medical Research Council (UK) MR/J002739/1, the Commission of European Communities Seventh Framework Programme (Collaborative Project Grant Agreement no. 22963, Mood Inflame) and the NIHR Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King’s College London.
TF01

ATOMOXETINE, A TREATMENT FOR ADHD, REDUCES IMPULSIVITY AND HYPERACTIVITY, BUT NOT INATTENTIVENESS IN NEUROKININ-1 KNOCKOUT MICE

Pillidge K, Dept of Neuroscience, Physiology and Pharmacology, University College London, Medical Sciences Bldg, Gower St London, WC1E 6BT, katharine.pillidge.11@ucl.ac.uk
Porter AJ(1), Vasili T(1), Heal DJ(2), Stanford SC(1)(1) Dept of NPP, UCL, Gower St, London, WC1E 6BT (2) RenaSci Ltd, BioCity, Pennyfoot St, Nottingham, NG1 1GF

Mice with functional ablation of substance P-preferring neurokinin 1 receptors (NK1R-/-) display neurochemical and behavioural abnormalities resembling those seen in Attention Deficit Hyperactivity Disorder (ADHD). These include: locomotor hyperactivity in the Light-Dark Exploration Box (LDEB), and impulsivity and inattentiveness in the 5 Choice Serial Reaction-Time Task (5-CSRTT) (Yan et al., 2011, PLoS One, Mar7;6(3) e17586). Here, we investigated whether the selective noradrenaline reuptake inhibitor, atomoxetine, which is approved for the treatment of ADHD, reduces hyperactivity and improves cognitive performance. Following training in the 5-CSRTT, wildtype and NK1R-/- mice were tested once-weekly, using a variable inter-trial interval (VITI), 30 min after treatment with vehicle (saline, 10ml/kg), atomoxetine (0.3, 3 or 10mg/kg, i.p.) or no injection. Each treatment was given to each mouse once, as a counterbalanced sequence. Atomoxetine reduced impulsivity in NK1R-/- mice [10mg/kg vs. vehicle, P=0.013] but not wildtypes. However, atomoxetine lengthened reward latencies in both genotypes [drug: F(3,55)=10.59, P<0.001], but had no effect on response latencies [drug: F(4,74)=1.85, P=0.128]. Atomoxetine had no effect on inattentiveness in either genotype. A separate cohort of mice was tested in the LDEB. Mice were transferred to the light zone of the LDEB 30 min after treatment with vehicle, atomoxetine (1, 3 or 10mg/kg, i.p.) or no injection. NK1R-/- mice were hyperactive in the light zone [NI: WT vs. NK1R-/-, P=0.004], a behaviour which was attenuated by atomoxetine treatment [drug: F(3,31)=3.84, P=0.019]. Atomoxetine reduced the number of returns to the light zone in both genotypes [drug: F(3,31)=4.13, P=0.014], but had no effect on time spent in the light zone [drug: F(3,31)=0.09, P=0.964], suggesting that the reduction in hyperactivity was not a secondary consequence of an effect on emotionality. We conclude that atomoxetine may be most efficacious in patients with the hyperactive-impulsive subtype of ADHD. This work was funded by the MRC (UK) and RenaSci Consultancy Ltd.

TE09

VIEWS ON RECENT RECOMMENDATIONS ABOUT BENZODIAZEPINES: QUANTITATIVE AND QUALITATIVE SURVEY

Brandish EK, Dept of Psychiatry, Univ of Southampton, Academic Centre, College Keep, 4-12 Terminus Terrace, Southampton, Hants SO143DT, ebrandish@hotmail.com
Baldwin D, Univ Dept of Psychiatry, Academic Centre, College Keep 4-12 Terminus Terrace, Southampton, Hants SO143DT

Introduction: Understanding of the potential risks and benefits of prescribing benzodiazepines has increased over time, as has understanding of potential hazards and benefits of prescribing alternatives (such as SSRIs, SNRIs or pregabalin, in patients with anxiety disorders). A working group drawn from the BAP and from the Psychopharmacology Special Interest Group of the Royal College of Psychiatrists (now defunct) published recommendations about benzodiazepine prescribing in clinical practice in November 2013 (Baldwin DS et al. J Psychopharm, 2013; 27: 967-971). Given the sometimes controversial nature of the debate about use of benzodiazepines in psychiatric practice, efforts were made to seek opinions on these recommendations from clinicians who might prescribe them, using quantitative and qualitative methods. Method: A 10-item questionnaire was developed using a Likert scale to gain views on each of the listed recommendations. Respondents were invited to read the statement and to register their agreement or disagreement for each recommendation: and to take the opportunity for providing any free text comments, (negative, neutral or positive) at the end of the questionnaire. The statement and questionnaire were both included within delegate packs at two meetings organised by the BAP (January, and February, 2014). Results: A total of 169 individuals completed the questionnaire. There were 14 missing data items across all questionnaires. Overall, there was broad agreement across the 10 statements: endorsement of individual items ranging between 79.0% and 98.3% agreement (slightly or completely). Registered disagreement ranged between 1.2% and 14.4%: those opting to neither agree nor disagree ranged from 0.6% to 7.2% across individual items. Free text comments were made by 53 individuals: 13 wrote positive comments about the statements, 12 provided more negative comments, and 28 made essentially neutral statements. When registering attitudes to benzodiazepines, 19 made positive comments, 12 made negative comments, and 22 provided neutral comments. Thematic analysis of the free text comments highlighted the need for clinical decision making on an individual patient basis, taking into account the relative risks and benefits of benzodiazepine treatment as a prominent theme. Conclusions: It would appear that the recommendations within the statement are broadly acceptable and relevant to prescribing psychiatrists. Respondents to the questionnaire considered there was still a role for benzodiazepines in some patients, but highlighted the importance of clinical judgement in their use. No sources of funding were received in the preparation of this work. Dr Brandish is funded by the NIHR Academic Clinical Fellowship scheme.
The ADHD treatment, guanfacine (an alpha2A-adrenoceptor agonist) alleviates spatial working memory deficits in non-human primates (Arnsten et al., 1988, J Neurosci, 8:4287-4298) and mice (Franowicz et al., 2002, J Neurosci, 22:8771-7). Mice lacking neurokinin-1 receptors (NK1R-/-), the preferred receptor for substance P, display neurochemical and behavioural abnormalities resembling those seen in Attention Deficit Hyperactivity Disorder (ADHD), including hyperactivity, inattention and impulsivity (Yan et al., 2011, PLoS One, Mar7;6(3):e17586). Patients with ADHD also show impairments in spatial working memory (Yancey et al., 2013, J Abnorm Child Psychol, 41: 891-900). Here, we investigated whether guanfacine improves spatial memory and/or object recognition in NK1R-/- and wildtype mice in a novel object recognition task. Mice were habituated to the test arena individually for 30 min on day 1. On day 2, they were treated with guanfacine (0.1mg/kg, i.p., dose based on previous findings) or vehicle (saline, 10ml/kg), 30 min before transfer to the test arena containing two identical objects. Mice were allowed to explore the objects for 10 min, before being returned to their home cage. After 1 h, mice were returned to the arena, where one object had been replaced with a new object (recognition test), or one of the identical objects had been moved to the opposite end of the arena (spatial test). Behaviour during the test was recorded on video and scored blind. Both genotypes spent more time exploring the novel object/location \[recognition: F_{0.12}=73.84, P<0.001\; \text{location: } F_{0.12}=114.59, P=0.001\]; i.e. they displayed intact recognition and spatial memory. However, guanfacine facilitated spatial memory in NK1R-/- mice, only \[\text{Veh vs. GFC0.1: } P=0.01\], but had no effect on recognition memory. We next tested another (non-selective) alpha2-adrenoceptor agonist, medetomidine (1, 3 and 10mg/kg, i.p.), in the spatial memory test. The effects of medetomidine were bidirectional; a low dose (1mg/kg) facilitated spatial memory in wildtypes \[\text{Veh vs. MED1: } P=0.052\], but a high dose (10mg/kg) attenuated spatial memory in wildtypes \[\text{Veh vs. MED10: } P=0.037\]. Neither dose affected the spatial memory of NK1R-/- mice.

We conclude that the difference between the two alpha2-adrenoceptor agonists can be attributed to differences in their pharmacodynamics. These findings are supported by previous reports suggesting alpha2-adrenoceptor agonists, especially guanfacine, relieve deficits in spatial memory. This work was funded by the MRC (UK) and RenaSci Consultancy Ltd.

Mice lacking functional neurokinin-1 receptors (NK1R-/-) display behavioural abnormalities seen in Attention-Deficit Hyperactivity Disorder (ADHD): hyperactivity, impulsivity and inattentiveness. Typical symptom profiles differ in male and female patients with ADHD, with more males than females presenting as the Hyperactive/Impulsive subtype. The angiotensin-converting enzyme (ACE) inhibitor, captopril, has cognitive enhancing effects (e.g.: Rhagavendra et al., 2001, Neuropeptides, 35:65-9), but there are sex differences in ACE activity (Komukai et al., 2010, Fundam Clin Pharmacol, 24:687-98). Captopril prevents hyperactivity in male NK1R-/- mice (Yee et al., 2008, Abs Supp J Psychopharmacol, 22:A79). Here, we compared the hyperactivity of male and female NK1R-/- mice and investigated whether captopril ameliorates the behavioural abnormalities of NK1R / mice in the light/dark exploration box (LDEB) and 5-Choice Serial Reaction-Time Task (5-CSRTT). We investigated the effects of captopril on the locomotor activity of male and female NK1R-/- mice in the LDEB. Following 60 min habituation to the dark zone, animals received either no injection (‘NI’), or an i.p. injection of saline or captopril (10 or 25 mg/kg) \(N=6\). 30 min later, they were transferred to the light zone and their behaviour in both zones monitored for 30 min. A separate batch of male wildtype and NK1R-/- mice was trained to criterion in the 5-CSRTT (\(N=12\); Yan et al., 2011, PLoS ONE, 6:e17586). Animals were then tested once weekly, using a variable intertrial interval \(2, 5, 10\) and \(15\) s) and a long intertrial interval \(10\) s). In both tests, animals received either no injection (‘NI’), or an i.p. injection of saline or captopril \(5, 10\) or \(25\) mg/kg). Every animal experienced each treatment once, in a counterbalanced sequence. Data were analysed using split-plot ANOVA, with post-hoc (LSD) pairwise comparisons. In the LDEB, the hyperactivity of male NK1R-/- mice was not present in females. Both doses of captopril prevented hyperactivity of male NK1R-/- mice \(P<0.05\), but neither dose affected the behaviour of male wildtype mice, or female mice of either genotype. In the 5-CSRTT, the greater impulsivity of NK1R / mice was prevented by \(10\) mg/kg captopril in both tests \(\text{LSD: } P<0.05\). Captopril did not affect the performance of wildtype mice in the 5-CSRTT, in either test. These findings are consistent with sex differences in ACE activity, and support evidence that captopril augments cognitive function. The possibility that ACE inhibitors offer a novel therapeutic treatment of ADHD (particularly the Predominantly Hyperactive/Impulsive subtype) merits further investigation. AP is an MRC PhD scholar.
Impulsive behaviour, simply defined as a tendency to act prematurely and without forethought, spans several behavioural domains from impaired inhibitory control to an intolerance of delayed rewards. Impulsivity is commonly observed in various neuropsychological disorders including schizophrenia and attention-deficit hyperactivity disorder (ADHD) and may contribute to the addiction process. Dysfunctional glutamatergic signalling has consistently been implicated in such disorders. Therefore, targeting the glutamatergic system pharmacologically may be therapeutically useful in modulating impulsive behaviour in humans. In this study, we investigated the role of glutamate in behavioural inhibition in male Lister Hooded rats, weighing 250-300 g at the start of the study, by focusing on the role of mGluR4 in modulating premature responding in the five-choice serial reaction time task (5-CSRTT). Following a high-throughput screening campaign, we selected and fully characterised a positive allosteric modulator of mGluR4, Cpd11. Following 5-CSRTT training, we tested the effect of Cpd11 pre-treatment on 5-CSRTT performance. The dose range selected (0-80 mg/kg) was based on locomotor activity assessment. The main findings demonstrate that Cpd11 has selective, mGluR4 PAM activity with an EC50 ~ 1µM (106% Glu max) and at 10 µM exerts no activity of ≥50% on 68 different receptor targets. In addition, Cpd11 is orally bioavailable and penetrates the CNS efficiently. Plasma and brain tissue concentrations reached 11.6 and 33.8 µM respectively following Cpd11 administration (30 mg/kg, p.o); brain:plasma ratio ~ 2.9. Cpd11 reached a concentration of 0.7 µM in the CSF (East et al., 2010, Bioorganic & Medicinal Chemistry Letters, Volume 20, Pages 4901-4905). A reduction in locomotor activity was observed at 100 mg/kg (main effect of dose p<0.001, post hoc test p<0.01, n=5) indicating the maximal dose limit. Behaviourally, Cpd11 robustly, dose-dependently increased premature responding on the 5-CSRTT. A maximal effect was observed at 60 mg/kg (main effect of dose p<0.01; dose x vehicle p<0.01, n=10). Interestingly, Cpd11 also dose-dependently decreased perseverative responding, an index of compulsive behaviour, on the 5-CSRTT. Again, a maximal effect was observed at 60 mg/kg (main effect of dose p<0.05; dose x vehicle p<0.01). These data indicate that mGluR4 may modulate different aspects of response inhibitory control in an opponent manner, thereby highlighting the neural independence of impulsive and compulsive behavioural endophenotypes. Complete Financial Sponsorship by Boehringer Ingelheim Pharma GmbH & Co. KG, Div. Research Germany, Birken­dorfer Strasse 65, 88397, Biberach an der Riss, Germany

The 5-choice continuous performance task (5C-CPT) is a translational task for assessing impulsivity, sustained attention and vigilance and is based on the human CPT. The dopamine D4 receptor (DRD4) has been genetically linked to ADHD and also mediates prefrontal cortex response to the first line pharmacological treatment for ADHD, methylphenidate. Catechol-O-Methyl Transferase (COMT) is responsible for approximately 60% of dopamine catabolism in the prefrontal cortex and reduced function is another genetic risk factor for ADHD. The aim of this study was to test first line pharmacological treatment for ADHD, methylphenidate. Catechol-O-Methyl Transferase (COMT) is responsible for approximately 60% of dopamine catabolism in the prefrontal cortex and reduced function is another genetic risk factor for ADHD. The aim of this study was to test first line pharmacological treatment for ADHD, methylphenidate.

THE D4 RECEPTOR AGONIST (A412997) AND COMT INHIBITOR (TOLCAPONE) IMPROVE ATTENTION AND RESPONSE INHIBITION IN A RODENT MODEL OF ADULT ADHD

Hayward A, Manchester Pharmacy School, Univ of Manchester, Manchester, M13 9PT, andrew.hayward@postgrad.manchester.ac.uk
Tomlinson A(1), Grayson B(1), Marsh (S1), Neill J(1) (1) Manchester Pharmacy School, Univ Of Cambridge, Downing St, Cambridge, CB2 3EB (3) Dept of Psychiatry, Univ Of Cambridge, Downing St, Cambridge, CB2 2QQ

The 5-choice continuous performance task (5C-CPT) is a translational task for assessing impulsivity, sustained attention and vigilance and is based on the human CPT. The dopamine D4 receptor (DRD4) has been genetically linked to ADHD and also mediates prefrontal cortex response to the first line pharmacological treatment for ADHD, methylphenidate. Catechol-O-Methyl Transferase (COMT) is responsible for approximately 60% of dopamine catabolism in the prefrontal cortex and reduced function is another genetic risk factor for ADHD. The aim of this study was to test the effects of the selective DRD4 agonist A-412997 and tolcapone, a COMT inhibitor, on vigilance, and sustained attention, in the 5C-CPT in rats separated into high attentive (HA) and low attentive with response inhibition deficits (ADHD-C) subgroup. Female Lister-hooded rats were trained in the 5C-CPT to reach a stable baseline, as described in Barnes et al. (Psychopharmacology, 2012: 220, 129-141), then separated into HA or ADHD-C groups using accuracy (> or < 90%; sustained attention), sensitivity index (SI; > or < 0.3; vigilance) and probability of false alarms (p[FA]; < or > 0.5; impulsive action). Half of each subgroup was randomly selected to receive A-412997 (0.1, 0.3, 1.0 µmol/kg or saline i.p.) or tolcapone (3, 10, 15 mg/kg or saline i.p.) 30 min prior to testing with an increased variable inter-trial-interval (5-10s). Data was analysed using repeated measures ANOVA with LSD planned comparisons. A-412997 significantly increased SI (p<0.05,<0.01) and reduced p[FA] (p<0.01,<0.001) at 0.3 and 1.0 µmol/kg in ADHD-C animals, however, at1.0 µmol/kg responsiveness index was significantly reduced (p<0.05) suggesting change in SI may be due to a different response strategy at this dose. Tolcapone significantly increased accuracy in ADHD-C animals at 10 (p<0.01) and 15 mg/kg (p<0.05) and reduced p[FA] at 15 mg/kg (p<0.01). In contrast, HA animals’ accuracy was significantly reduced at 15 mg/kg (p<0.05). At 15 mg/kg, tolcapone significantly increased SI (p<0.05) in ADHD-C animals, and decreased it in HA animals (p<0.01). The significant difference in attentive and impulsive measures supports ADHD-C animals as a model of combined type ADHD. In this model A-412997 and tolcapone improved response inhibition and vigilance deficits. Tolcapone also improved accuracy in ADHD-C animals, in contrast accuracy and SI were reduced in HA animals at the highest dose. COMT and DRD4 warrant further investigation as a therapeutic target for adult ADHD. Sources of financial sponsorship: This work is supported by the University of Manchester Declaration of interest from: JCN has received expenses to attend conferences and fees for lecturing and consultancy work (including attending advisory boards) from the manufacturers of various psychiatric drugs.

ABSTRACTS
TF06

ADULT ADHD PATIENTS STABILIZED ON MEDICATION SHOW LESS EMOTION RECOGNITION DEFICITS THAN UNMEDICATED PATIENTS BUT MORE THAN HEALTHY CONTROL SUBJECTS

Tomlinson A, Manchester Pharmacy School, Univ of Manchester, Stopford Bldg, Oxford Rd, Manchester, M13 9PT, anneka.tomlinson@postgrad.manchester.ac.uk

Baskind R(1) Johnson J(2) Whitaker G(3) Marshall KM(3) Neill JC(3) (1) Leeds and York Partnership NHS Foundation Trust, Malham House, Leeds (2) 5 Boroughs NHS Foundation Trust, Leigh Infirmary, Avenue Day Hospital (3) Dept of Psychology and Manchester Pharmacy School

Introduction: Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder now known to persist into adulthood. ADHD comprises symptom clusters of inattention, impulsivity and hyperactivity. Both children and adults with ADHD show impaired in interpersonal and social functioning compared to the normal population. Deficits in emotional recognition during childhood have been proposed to underpin the social dysfunction in ADHD. To date little is known about nonverbal emotion recognition in adults with ADHD, in particular with respect to the symptom subtypes observed within ADHD. Aims: 1. To compare emotion recognition of treated with untreated adult patients with ADHD and treated patients and untreated patients with healthy controls. 2. To compare the emotion recognition abilities between the different subtypes of ADHD. Methods: Participants were recruited from two specialist NHS adult ADHD clinics in England. The sample consisted of 114 participants divided into three groups: ADHD treated (ADHD-T; n=38), ADHD untreated (ADHD-UnT; n=44), and healthy controls (n= 32), mean age - 29 years. All participants diagnosed with ADHD must have met the criteria outlined in DSM-IV. All ADHD participants completed a full self-report Connors Adult ADHD Rating Scale, WEISS-Global Impairment Rating Scale and five neurocognitive tasks using the Cambridge Automated Neuropsychological Test Battery (CANTAB). The Emotion Recognition Task (ERT) – CANTAB task, was used to assess emotion recognition. The ERT displays a series of faces and the participant must identify the emotion (happiness, sadness, anger, disgust, surprise and fear). Results: ANOVA also revealed that ADHD-UnT group made more errors when presented with faces displaying fear and anger, relative to healthy controls (p<0.001). Finally, the ADHD-T group made more errors when presented with faces displaying fear and anger, relative to healthy controls (p<0.01). Discussion: We have shown that adults with ADHD have impairments in facial emotion recognition in comparison to healthy controls. This study also suggests that standard ADHD medication (methylphenidate and/or atomoxetine), improves emotion recognition, specifically the negative emotions; anger and disgust recognition. These findings highlight the importance of social cognition as a target for treatment and the importance of social functioning in adults with ADHD. Future directions: Further analysis will focus on correlations between the different ADHD subtypes, and specific emotion recognition deficits and level of functional impairments. This study was funded by the University as part of a PhD programme

TF07

PRESCRIBING PRACTICE FOR ADHD IN CHILDREN, ADOLESCENTS AND ADULTS IN THE UK

Paton C, Centre for Mental Health, Imperial College, London, W6 8LN, Carol.Paton@oxleas.nhs.uk

Adroer R(2) Barnes TRE(1,2) 1. Centre for Mental Health, Imperial College, London W6 8LN 2. CCQI, Royal College of Psychiatrists, London E1 8BB

NICE guidance on ADHD treatment (CG72, 2008), recommends both behavioural therapies and certain medication (including methylphenidate, atomoxetine and dexamfetamine). Adverse drug effects are uncommon but warrant continued monitoring. Before treatment initiation, a medical history should be taken with particular reference to cardiovascular risk factors and blood pressure and pulse rate should be recorded and then monitored during therapy. Prescribing practice with ADHD drugs was assessed in a national clinical audit in 2013, as part of a POMH-UK quality improvement programme. A customised report including benchmarked data reflecting clinical performance against best practice standards was subsequently sent to each of the 48 mental health Trusts that participated, to prompt reflection by clinicians on their practice and stimulate action plans to tackle areas where performance fell short. The total audit sample comprised 5,479 patients with a diagnosis of ADHD: 57% from CAMHS services, 6% from paediatric services and 37% from adult mental health services. 4,851 (89%) of the total sample were prescribed medication for ADHD, of whom 87% were taking a methylphenidate preparation. There was good adherence by CAMHS and paediatric services to best practice standards for measurement of height, weight, blood pressure and pulse before starting drug treatment. However, in those 16 years of age or younger, these measures were often not documented on growth and centile charts, perhaps partly reflecting lack of availability of these charts. CAMHS and paediatric services also performed relatively well conducting early, on-treatment checks of tolerability. Further, the majority of patients receiving longer-term treatment with ADHD medication within these services had had at least one documented measure of height, weight, blood pressure and pulse in the past year. However, while a practice standard of two measures of height and weight during the previous year was met for just over half the patients, a standard of four measures of BP and pulse was met in only 20%. This may partly reflect clinicians’ uncertainty about the need for such frequent monitoring and/or lack of clarity about monitoring responsibility and communication of findings between secondary and primary care. In both paediatrics and CAMHS, the use of growth and centile charts tailed off over time. This limits the ability of clinicians to assess any adverse effects of medication on growth or cardiovascular parameters. Adult services fared less well overall with respect to compliance with standards relating to baseline measures, early-on treatment monitoring and the monitoring of longer-term treatment. POMH-UK is funded solely via subscription from member Trusts and other healthcare organisations
TF08

ANXIETY IN PREGNANCY AND ADHD IN CHILDREN, A SYSTEMATIC REVIEW OF THE LITERATURE

Bolea B, Univ of Bristol, Suite 1204, Jasmine Court, Camana Bay, KY1-1006, blanca.bolea@gmail.com
Davies SJC Centre for Addiction and Mental Health CAMH (PACE CLINIC) Toronto, ON M5S 2S1 Room: Jan-41

Introduction- The fetal programming hypothesis proposes that environmental factors impacting the mother during pregnancy programme the child’s metabolic pathways for better adjustment to the environment at birth. Accumulating evidence suggests that fetal programming may occur in the brain. ADHD is one of the most commonly diagnosed mental health conditions in childhood. Anxiety in the pregnant mother could potentially alter neuronal development and lead to behavioural problems in the child. Methods- We performed a systematic review of mother–child prospective cohort studies focusing on the effects of anxiety during pregnancy and its correlation with ADHD symptomatology in the children (following the PRISMA statement). PubMed, PsychINFO, Web of Science, Embase, Biosis and Medline were searched. Only studies with validated scales for anxiety and ADHD were considered. Results- Seven cohort studies meeting the above criteria were identified. Two studies used the Crown-Crisp Experiential Index for anxiety in pregnancy and the Strengths and Difficulties Questionnaire for symptoms in children. Five studies used the State Trait Anxiety Inventory in pregnancy, two of those performed the Child Behavioral Checklist to assess children, another two used an ad hoc continuous performance test, and one study used the Bayley Psychomotor Scale. One study (Van Den Bergh, 1990, Pre and perinatal psychology, 5(2), 119-128) found no correlation between anxiety in pregnancy and hyperactivity symptoms, the other six studies found some evidence of association. O’Connor et al (2002, J Am Acad Child Adolesc Psychiatry;41(12):1470-7) reported ORs of 1.56 (boys) and 1.51 (girls) (95% CI 1.02-2.41 and 1.22-2.81 respectively), and a second paper from the same group (2003, O’Connor et al, J Child Psychol Psychiatry. t;44(7):1025-36) reported OR of 1.91 for girls and 2.16 for boys, (95% CI 1.26-2.89, 95% CI 1.41-3.30 respectively). De Brujin et al (2009, Early Hum Dev. ;85(5):319-24) found moderate to weak correlations between the anxiety measure and the CBCL scores (R2=.23, p<.01; β=.36, p<.05). Three studies on the Van den Bergh cohort showed an effect only when anxiety was high on weeks 12 to 22 of pregnancy (F(1,52)=1.31, p=0.257); this association did not persist when children were assessed at 15 years of age. Limitations - Most cohorts had high attrition which may have attenuated the effect. Five studies did not control for depression in mothers. Conclusion- Fetal programming of the brain remains an intriguing hypothesis. Based on our systematic review there is some evidence of a small effect of prenatal anxiety in child ADHD. Disclosure - No funding was required for this research.

TF09

REDUCED STRIATAL SEROTONIN 5-HT2A RECEPTOR LEVELS IN THE SUBCHRONIC VALPROATE MODEL

Skovborg MMS, CFIN, Aarhus University Hospital, Nørrebrogade 44, Bldg 10G, 5th Floor 8000 Aarhus C Denmark, 8000 , maria.skovborg@studmed.au.dk

Bertelsen F, Weikop P, Scheel-Krüger J, Møller A, Landau AM CFIN, Aarhus University Hospital, Nørrebrogade 44 Building 10G, 8000 Aarhus C, Denmark

Introduction: Alterations in the serotonin (5-HT) system are often detected in patients with Autism Spectrum Disorders (ASD). Prenatal exposure to Valproate (VPA) is associated with ASD in the offspring. We have recently developed a novel animal model of autism in which pregnant rats were exposed to subchronic doses of VPA and we have detected increased neuronal cell number and behavioural deficits in the offspring of VPA compared to saline-treated rats. Previous data from our group demonstrated decreased striatal 5-HT levels in rats prenatally exposed to VPA compared to controls. In light of this finding, the aim of the current study is to further investigate the serotonin system with focus on the 5-HT2A receptor and the serotonin transporter (SERT). Methods: Pregnant Wistar rats were treated with VPA (20 or 100 mg/kg) or saline from day 12 until the end of pregnancy. Brains from the male offspring (n=7/group) were removed and fresh frozen at 50 days of age and then sliced into 20 μm thick sections. We performed in vitro autoradiography of striatal 5HT2A receptors using [3H]Ketanserin as the radioligand and mianserin to assess non-specific binding. We assessed striatal SERT levels using [3H]DASB as the tracer and citalopram to detect non-specific binding. Statistics were done on the specific binding values using a one-way analysis of variance (ANOVA) followed by a Bonferroni post hoc test. Results: The 5-HT2A receptor binding was significantly decreased in dorsolateral and ventrolateral striatum in rats prenatally exposed to VPA compared to saline controls (p<0.05 and p<0.01 respectively). The post hoc test revealed that the decrease in dorsolateral striatum was only significant for the rats exposed to 20 mg/kg/day whereas the decrease in ventrolateral striatum was significant in both VPA-groups. However, VPA did not induce changes in striatal [3H] DASB binding. Conclusions: The lower 5-HT2A receptor binding combined with reduced levels of 5-HT in striatum indicate a down-regulation of the serotonin system in the VPA-exposed rats consistent with imaging studies in human in which 5-HT2A receptor levels are altered. The lack of difference in SERT-binding is in contrast to human imaging studies which detects reduced SERT availability, however methodological and species differences may account for the differences in data. The changes at the receptor and not the transporter level in our study may suggest changes in serotonin metabolism and release coupled to 5-HT2A receptor regulations. Funded by Aarhus University and Aarhus University Hospital.
DISORDER-SPECIFIC PERFORMANCE AND BRAIN FUNCTION IN TEMPORAL DISCOUNTING IN YOUTH WITH AUTISM SPECTRUM DISORDER RELATIVE TO OBSESSIVE COMPULSIVE DISORDER

Carlisi CO. Child and Adolescent Psychiatry, Inst of Psychiatry, King’s College London, 16 De Crespigny Park London, SE5 8AF, christina.carlisi@kcl.ac.uk
Norman L(1), Murphy C(1,2), Christakou A(1), Chantiluke K(1), Murphy D(2), Rubia K(1) (1) Dept of Child and Adolescent Psychiatry, Inst of Psychiatry, King’s College London, SE5 8AF (2) Dept of Forensic and Developmental Sciences, Inst of Psychiatry, King’s College London, SE5 8AF

 Patients with Autistic Spectrum Disorder (ASD) and patients with Obsessive Compulsive Disorder (OCD) both exhibit behavioural and neurofunctional deficits in executive functions including reward processing and inhibitory control. However, little is known about reward-related decision-making and delay aversion processes in these disorders. Temporal Discounting (TD) is a well-validated measure of an individual’s valuation of reward as a function of time delay and has been associated with impulsiveness. This study aims to elucidate disorder-specific differences in performance and neurocircuitry during TD between individuals with ASD and individuals with OCD relative to healthy controls. Differences in behaviour and neural substrates of TD may provide crucial insight into disorder-specific phenotypes of ASD and OCD and aid in our understanding of common and distinct neural and behavioural changes in each disorder. Twenty-nine adolescent males diagnosed with ASD and eleven with OCD were matched with eighteen healthy controls and performed a TD task using functional magnetic resonance imaging (fMRI). Participants were asked to serially choose between winning a smaller amount, between £0 and £100, of money immediately or winning a larger amount (always £100) in one week, month, or year. The immediate amount was adjusted per subject in an algorithm to converge on an individual indifference amount for each time delay, considered by the subject as equivalent to the delayed reward. The algorithm ensures equal numbers of delayed and immediate choices (Christakou et al., 2011. Neuroimage, 54:1344-1354). The dependent variable is the steepness of TD, k, which is calculated based on a hyperbolic function. fMRI analyses test for group differences in the contrast of delayed vs. immediate choices. A one-way ANOVA revealed a between-group difference in TD, as measured by mean k scores (F(2,53)=3.59, p=0.035) across all delays. Post-hoc analyses revealed that the autism group had a steeper discounting rate than the control group (p<0.05) but not the OCD group (p=0.23), which did not differ from controls (p=1.00). The fMRI analysis revealed a correlation in the ASD group between caudate activation and mean k values (r=-.499, p=0.005). Patients with autism but not those with OCD demonstrate a steeper rate of TD, suggesting that the subjective value of a reward is worth less for ASD patients than for controls if reward receipt is delayed, possibly reflecting impulsiveness. Moreover, this impulsivity measure relates to differences in reward-based neural circuitry in autism. These results provide promising insight into a possible differentiating mechanism of reward-based decision-making between OCD and ASD. -- This study was supported by grants from the Medical Research Council (MRC G0300155 to KR and the Medical Research Council UK Autism Imaging Multicentre Study (MRC AIMS) to DGM) and the EU IMI AIMS network (to DGM), receiving support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no. 115300, which includes financial contributions from the EU Seventh Framework Programme (FP7/2007-2013). Christina Carlisi is supported by a PhD studentship from the NIHR Biomedical Research Centre.

RODENT MODELS OF IMPULSIVITY: INFORMING THE NEUROBIOLOGICAL MECHANISMS OF ADDICTION RISK

Jupp B. Dept of Psychology and Behavioural and Clinical Neuroscience Inst, The University of Cambridge, Downing St Cambridge, CB2 3EB, bj251@cam.ac.uk

Impulsivity describes an enhanced tendency for premature, unduly risky and poorly conceived actions and as a behavioral trait is associated with a number of psychopathological disorders including attention deficit hyperactivity disorder (ADHD) and substance use disorder (SUD). Studies in rats with intrinsically elevated levels of premature responding on the 5-choice serial reaction time task (5CSRTT) confirm the relationship of impulsivity to enhanced addiction related behaviours and implicate dysfunction in the corticostriatal network, particularly involving dopaminergic neurotransmission, in the expression of this behavioural trait. Intriguingly, cocaine appears to remediate the expression of impulsivity in these rats, akin to the treatment of ADHD by stimulant medication. It is not clear whether expression of impulsivity or cocaine’s effect to remediate this behaviour is related to alterations in dopamine receptor function and further whether stimulant medications for ADHD work in a similar manner. Here we report a series of studies using neuroimaging approaches and complementary neurochemical analyses to investigate mechanisms underlying the expression of impulsivity, its remediation by cocaine and the related ADHD therapeutic methylphenidate, and whether these mechanisms may relate to the enhanced substance abuse related outcomes observed in highly impulsive (HI) rats. These studies implicate a role for reduced dopaminergic function within the ventral striatum in impulsivity, reflecting reduced dopamine transporter, D1 and D2/3 receptor autoradiographic binding. Both cocaine and methylphenidate were capable of correcting the reduction in D2/D3 binding observed in HI rats, as measured by [18F]-Fallypride positron emission tomography. This effect correlated with a reduction in impulsivity by cocaine, however this did not generalize to methylphenidate, suggesting an alternate mechanism may underlie this effect. In-keeping with this hypothesis, magnetic resonance imaging additionally identified reduced grey matter density within the ventral striatum of HI rats. This reduction in density was found to correlate with reductions in protein markers for GABAergic neurotransmission and dendritic spines, both of which represent potential candidates through which cocaine and methylphenidate may remediate impulsivity and further through which this trait predicts enhanced drug related behaviours. This work was supported by the Medical Research Council (MRC G0701500) and by a joint award from the MRC and Wellcome Trust in support of the Behavioural and Clinical Neuroscience Institute at Cambridge University. The author also acknowledges funding from the MRC Imperial College-Cambridge University-Manchester (ICCAM) strategic addiction cluster and grants from the AXA Research Fund and the Australian National Health and Medical Research Council (1016313).
EXAMINATION OF THE ROLE OF AN INFLAMMATORY PREDISPOSITION IN THE PATHOPHYSIOLOGY OF DEPRESSION: INSIGHTS FROM A “MULTIPLE HIT” ANIMAL MODEL

Egeland M, IOP, King’s College London, 125 Coldharbour Lane, SE5 9NU, martin.egeland@kcl.ac.uk

An accumulating number of studies indicate that inflammation is involved in the pathophysiology of depression. Specifically, increased levels of inflammatory biomarkers are found in depressed individuals and, in addition, inflammatory cytokines used in the treatment of certain diseases induce depressive symptoms as a side effect in a large number of patients (For review see Haroon et al. 2012. Neuropsychopharmacology Jan;37(1):137–62). Finally, clinical results demonstrate that both adult and early-life stressors are strongly associated with increased inflammation (Danese et al. 2008. Arch Gen Psychiatry 65:409–415). In an effort to further decipher the potential role of inflammation in the development of depression, we have developed an animal model that investigates how early-life inflammation potentially creates a vulnerability that predisposes the brain to depression. Depressive symptoms are hypothesized to precipitate when individuals with this inflammatory predisposition are exposed to additional pathological mechanisms, referred to as “environmental hits”. The hits thought to precipitate depression in adulthood in certain individuals include stress and lower levels of adult neurogenesis. In our studies we therefore investigated the effects of chronic stress and an experimentally induced decrease in adult neurogenesis as further environmental hits in combination with this inflammatory predisposition. Results from these experiments demonstrated that early-life inflammation resulted in altered peripheral levels of several cytokines and furthermore altered dynamics in response to experimentally induced immune activation that varied at different developmental stages. In addition, preliminary results from behavioral experiments indicate a pattern that shows a more pronounced behavioral effect of two environmental hits versus one in addition to the inflammatory predisposition. Though ongoing studies are required to verify this, these apparent additive effects may be representative of a vulnerability that is incurred by early-life environmental insults that may be an important aspect of the pathophysiology of depression. Acknowledgement: This research was funded by a grant from the Commission of European Communities Marie Curie actions and in part by grants from Janssen/J&J and Lundbeckfonden.

LONG LASTING STRESS-RELATED CHANGES IN THE BRAIN AND INCREASED RISK FOR PSYCHIATRIC DISORDERS: ROLE OF EPIGENETICS

Cattaneo A, Dept of Psychological Medicine, Lab of Stress, Psychiatry and Immunology, Inst of Psychiatry, King’s College London, The James Black Centre, Room 2-059, 125 Cold Harbour Lane, London, SE5 9NU, annamarie.cattaneo@kcl.ac.uk

It is well known that a history of early life stressful events increases the vulnerability to develop psychiatric disorders in adulthood, but the biological mechanisms underlying this association are yet not clear. This talk will focus on the role of childhood trauma in causing changes in specific molecular pathways that persist over time and are potentially responsible for increasing vulnerability to develop depression. By using a transcriptomic approach, we have found that, in a sample of otherwise healthy adult subjects, those exposed to childhood trauma (n=20), compared with non-exposed subject (n=20), show alterations in 140 genes, which belong mainly to inflammatory-related pathways, including cytokine-cytokine interaction, T cell activation, Inflammation chemokine- and cytokine-mediated, and B cell activation. The overall analysis confirms a pattern of increased inflammation, consistent with what we have previously shown in depressed patients (Cattaneo A, Gennarelli M, et al. Candidate genes expression profile associated with antidepressants response in the GENDEP study: differentiating between baseline ‘predictors’ and longitudinal ‘targets’. Neuropsychopharmacology 2013 Feb;38(3):377-85. doi: 10.1038/npp.2012.191. Epub 2012 Sep 19). In addition, we have used a hypothesis-based approach to examine the levels of serum- and glucocorticoid-inducible kinase 1 (SGK1), a glucocorticoid-dependent target gene involved in stress-induced reduction of neurogenesis (Anacker C, Cattaneo A, et. Role for the kinase SGK1 in stress, depression, and glucocorticoid effects on hippocampal neurogenesis. Proc Natl Acad Sci U S A. 2013 May 21;110(21):8708-13. doi: 10.1073/pnas.1300886110. Epub 2013 May 6.). In this clinical sample, SGK1 mRNA levels are higher in subjects with a history of childhood trauma (+30%, p<0.05) as compared with subjects without such experiences. Moreover, in a separate sample, depressed patients have higher SGK1 mRNA levels, both in those without exposure to early life trauma (n=18) (+25%, p<0.05), and even more so in those with exposure to early life stressful events (n=19)+50%, p<0.05). Similarly to these human samples, we have found that rats exposed to prenatal stress display a significant increased of hippocampal SGK-1 mRNA levels (+42%, p<0.005); this is present only when they reach adulthood (PND62), but not at earlier stages (PND7, PND21 and PND40), suggesting an epigenetic effect. Indeed, analyses across the animal and clinical samples confirm consistent stress-induced hypermethylation of the SGK1 gene, in corresponding sites. Our data suggest that stressful events occurring in early life cause persistent alterations in several biological processes, including inflammatory pathways and stress-related systems, which persist into adulthood and may be responsible for increased vulnerability to psychiatric disorders.
PD04

EFFECTS OF REPEATED SSRI ADMINISTRATION ON THREAT-RELATED PROCESSING IN A POPULATION AT RISK FOR PSYCHOPATHOLOGY: USING A VULNERABILITY MODEL TO UNDERSTAND ANTIDEPRESSANT TREATMENT MECHANISMS

Di Simplicio M, MRC Cognition and Brain Sciences Unit, 15 Chaucer Rd, Cambridge, CB2 7EF, Martina.DiSimplicio@mrc-cbu.cam.ac.uk
Doallo S1, Costoloni G2, Rohenkohl G3, Reinecke A4, Norbury R5, Nobre AC3, Harmer CJ4 1 Dept of Clinical Psychology & Psychobiology, Univ of Santiago de Compostela; 2 Neuroscience Dept, Psychiatry Section, Univ of Siena, Siena, Italy; 3 Dept of Experimental Psychology and Oxford Centre for Human Brain Activity, Univ of Oxford, UK; 4 Univ Dept of Psychiatry, Warneford Hospital, Oxford, UK; 5 Dept of Psychology, Univ of Roehampton, UK

Anxiety and depression are associated with changes in facial stimuli processing, which could contribute to the misinterpretation of ambiguous emotional stimuli typical of these disorders. Recent findings have shown that SSRI antidepressants modulate responses to emotional information early on in treatment in both healthy and clinical populations. In clinical practice SSRIs it remains unknown whether variable response to treatment depends on specific facets of anxiety or depression. Aim of our studies was to investigate the effects of short term repeated SSRI administration on threat-related stimuli, using a vulnerable population presenting traits of both high anxiety and low mood. Methods Individuals with high neuroticism traits based on scores above 16 on the Eysenck Personality Questionnaire neuroticism scale were randomly allocated to 7 days of either citalopram (20mg) or placebo in two studies. On the last day of treatment they completed a covert emotion processing task with happy, fearful and neutral faces presented for 500ms, and underwent a neurofunctional imaging scan or eye track recording of ocular movements. Participants in the eye tracking study also completed an overt emotion recognition task. Subjective affect ratings were collected during the intervention in both studies. Results In the neuroimaging study, the citalopram-treated group showed an increased response to fearful facial expressions compared to happy ones in a network of brain areas including the fusiform gyrus, temporal and prefrontal cortical areas. SSRI administration also increased the right amygdala response to all faces, regardless of the emotion. In the eye tracking study, the citalopram-treated group showed increased gaze maintenance over all faces, regardless of the emotion, compared to placebo and enhanced recognition of positive vs. negative facial expressions. Follow-up antidepressant administration longer ocular correlation of happy faces correlated positively with recognition of positive emotions. Effects on facial stimuli processing were shown in the absence of change in subjective measures of affect in both studies. Discussion Our findings suggest that SSRIs can modulate the ability to process socially relevant and potentially threat-related stimuli, by increasing the neural response to facial expression and by directly modifying ocular exploration of faces. Prolonged processing of facial expressions, in particular fearful ones, might lead to increased exposure to potentially anxiety provoking stimuli. This could contribute in time to better tolerance of feared stimuli and subsequent reduction of anxiety symptoms. It could also account for the so-called anxiogenic effect reported by some patients in the early stages of antidepressant treatment.

PW1

THE DMFPC-AMYGDALA CIRCUIT: A POTENTIAL NEUROPHARMACOLOGICAL TARGET FOR ANXIETY DISORDER TREATMENT AND DIAGNOSIS?

Robinson OJ, Institute of Cognitive Neuroscience, University College London, 17 Queen Square, London, WC1N 3AR, o.robinson@ucl.ac.uk

Diagnosis and treatment of mood and anxiety disorders is largely based on self-reported symptoms rather than an understanding of any underlying neurobiological mechanisms. This disconnect likely contributes to poor diagnostic specificity and treatment response. In this talk I will discuss one line of research attempting to bridge this symptom-mechanism divide. Specifically, I will provide an overview of my recent work attempting to track a circuit, informed by translational animal work, across its healthy and pathological states. I will present data suggesting that positive coupling between the amygdala and the dorsal medial prefrontal cortex (dmPFC) can drive elevated threat perception in stressed healthy individuals (Robinson et al 2012 Neuroimage), alongside related data from an adapted stressed-resting-state paradigm in healthy individuals (Vytal et al 2014 J Psychiatry Neurosci). Moreover I will argue that this same circuit is recruited at baseline in individuals with unmedicated social and generalised anxiety disorder and, in fact, that circuit recruitment correlates positively with self-reported trait anxiety symptomatology (Robinson et al, in submission). As such, the same circuit which is involved in adaptive threat responding in stressed healthy individuals may be hyperactive in pathological anxiety disorders. Thus, in accordance with contemporary approaches to psychiatric diagnosis, pathological anxiety may fall towards one end of a continuous spectrum, driven in part by this amygdala-dmPFC circuit. Finally, I will present evidence that the neuromodulator serotonin may inhibit recruitment of this circuit, thereby providing a potential mechanism by which selective serotonin reuptake inhibitors (SSRIs) might exert their anxiolytic and antidepressant effects (Robinson et al 2013, Neuroimage). I suggest that this may, in turn, ultimately lead to improved treatment targeting. Overall, however, I aim to provide an overview of an early-stage roadmap for delineating more mechanistic, neurobiologically-informed treatments and diagnoses for mood and anxiety disorders. OJR is supported by an MRC Career Development Award. Work was funded by the intramural program of the National Institute for Mental Health

Winner of the 2014 BAP Junior Nonclinical Psychopharmacology Award
PW2

HUMAN MODEL SYSTEMS OF SCHIZOPHRENIA

Ettinger U. Dept of Psychology, Univ of Bonn, Kaiser-Karl-Ring 9 53111 Bonn, Germany, ulrich.ettinger@uni-bonn.de

Introduction: Schizophrenia is a severe psychiatric illness whose neurobiology is not sufficiently understood. Current pharmacological treatments alleviate positive symptoms in most but not all patients and do not satisfactorily reduce negative or cognitive symptoms and produce many unwanted side effects. There is thus a significant unmet clinical need for new compounds that treat all symptoms of schizophrenia whilst causing no or only few side effects. A key problem in the development of such drugs is the high attrition rate of new compounds in surrogate patient populations in phase II and III studies. A promising approach to alleviate these difficulties is the use of experimental model systems, especially in combination with well validated, translational neurocognitive biomarkers. In this talk, I will present recent biomarker data from three putative human model systems.

Methods: We studied the widely used eye movement and prepulse inhibition (PPI) biomarkers of schizophrenia in healthy humans. The applied model systems included (i) the administration of ketamine, (ii) the investigation of highly schizotypal individuals and (iii) experimentally controlled sleep deprivation. Results: The face validity of the experimental model systems received support from evidence of subjective ratings: Ketamine led to an increase in the experience of derealisation whilst sleep deprivation increased self-ratings of perceptual distortions, cognitive disorganisation and anhedonia. In terms of biomarker performance, (i) ketamine impaired accuracy on a smooth pursuit eye movement task and increased the rate of inhibitory failures in an antisaccade task, the latter in males only. These effects were not reversed by the administration of risperidone. (ii) Highly schizotypal individuals displayed impaired inhibition in an antisaccade task compared to low schizotypals on placebo. Interestingly, high schizotypals showed a non-significant improvement with risperidone whilst medium schizotypal controls’ performance deteriorated with risperidone. (iii) Finally, 24-hour sleep deprivation led to impairments in smooth pursuit and antisaccade eye movements as well as a reduction in PPI, especially at shorter stimulus onset asynchronies (30 and 60ms).

Conclusions: The presented data are in agreement with previous studies from experimental phase II and III studies. A promising approach to alleviate these difficulties is the use of experimental model systems, especially in combination with well validated, translational neurocognitive biomarkers. In this talk, I will present recent biomarker data from three putative human model systems.

Winner of the 2014 BAP Junior Clinical Psychopharmacology Award

PW3

DOPE AND DOPAMINE: INVESTIGATING THE DOPAMINERGIC EFFECTS OF LONG-TERM CANNABIS USE IN HUMANS

Bloomfield MAP, Psychiatric Imaging Group, MRC Clinical Sciences Centre, Mansfield Bldg Hammersmith Hospital, Du Cane Rd London, W12 0NN michael.bloomfield@imperial.ac.uk

Background: Cannabis is a widely used recreational drug which is frequently consumed with tobacco. Users are at increased risk of mental illnesses including psychosis and there is some evidence that cannabis reduces motivation i.e. causes apathy. The mesolimbic dopaminergic system mediates the processing of incentive stimuli, which is modulated by cannabinoid signalling. Substance dependence and schizophrenia are both associated with dopaminergic dysfunction. It had been proposed, although never directly tested, that the links between cannabis use, schizophrenia and apathy are mediated by altered dopaminergic function, which would increase psychosis risk by creating a state of aberrant salience.

Methods: We used positron emission tomography to compare dopamine synthesis capacity (DSC) in 19 regular cannabis users who experienced cannabis-induced psychotic-like symptoms with 19 nonuser sex- and age-matched control subjects. To investigate the effects of tobacco on DSC, we also compared 15 cigarette smokers to 15 non-smoker matched controls. We investigated the relationship between DSC and apathy in 14 cannabis users. Lastly, we measured salience processing in 17 cannabis users compared to 17 controls.

Results: Compared to controls, cannabis users had reduced striatal DSC (effect size: .85; t36=2.54, p=.016) whilst moderate cigarette users did not (t28=.64, p=.53). The group difference in DSC in cannabis users, compared with controls, was driven by users meeting diagnostic criteria for cannabis abuse or dependence. DSC was negatively associated with higher levels of cannabis use (r=-.77, p<.001) and positively associated with age of onset of cannabis use (r=.51, p=.027), but was not associated with cannabis-induced psychotic-like symptoms. Levels of cigarette use were not related to DSC. Within cannabis users, striatal DSC was inversely correlated with subjective apathy (r=-.64, p=.015). There were no differences in behavioural measures of salience processing between cannabis users and controls. Within Cannabis users there was a significant effect of dependency/abuse diagnosis on implicit aberrant salience (F1,15=5.8, p=.03) and a significant relationship between cannabis-induced psychotic-like symptom severity and explicit aberrant salience (r=.61, p=.04). In an exploratory analysis, compared to controls, cannabis users exhibit a loss of relationship between implicit salience processing and striatal dopamine synthesis capacity (z=2.12, p=.03).

Conclusions: These findings indicate that chronic cannabis use is associated with reduced dopamine synthesis capacity and this may underlie reduced motivation associated with chronic cannabis use. Since moderate cigarette smoking is not associated with altered striatal dopamine synthesis capacity, these findings are unlikely due to tobacco. These findings question the hypothesis that cannabis increases the risk of psychotic disorders by inducing the same dopaminergic alterations seen in schizophrenia, although there is preliminary evidence that dopaminergic mechanisms of salience processing are indeed altered with cannabis use.

Winner of the 2014 BAP Senior Nonclinical Psychopharmacology Award
PW4

BRAIN INTERACTOMICS USING INTEGRATIVE IMAGING: A NEW APPROACH TO UNDERSTAND PSYCHOTIC AND AFFECTIVE DISORDERS?

Howes O, Box 67, Inst of Psychiatry, Camberwell, London, SE5 8AF, Oliver.howes@kcl.ac.uk
Selvaraj S, Mouchilianitis E, Kim E, Fusar-Poli P, Allen P

Background: Neural systems implicated in drug effects and brain disorders have typically been studied in isolation. We sought to determine the relationships between these systems underlying cognitive and emotional processes implicated in schizophrenia and affective disorders. Method: In a series of multi-modal imaging studies combining PET of dopamine and serotonin 1a function and MRI imaging techniques in the same individuals we studied the inter-relationship between neural systems underlying cognitive and emotional functions that are dysfunctional in psychotic and affective disorders. Results: Striatal dopamine function was linked to alterations in brain activation in fronto-temporal regions during working memory and executive tasks (r= 0.732, p<0.001) and this inter-relationship was significantly different between ARMS and controls (p<0.0001). Transition to psychosis was linked to greater sub-cortical-frontal connectivity, and reduced topographical centrality. Striatal D2 antipsychotic occupancy was associated with reduced frontal metabolism. Lower serotonin 1a receptor availability in the raphe was associated with greater amygdala activation to fearful, but not happy, stimuli (r=0.8, p<0.001). Availability of raphe 5-HT1A receptors positively correlated with amygdala connectivity with frontal and occipital cortical regions involved in emotional processing. Conclusion: These findings provide evidence for the importance of interactions between serotonin 1a function and amygdala-frontal function underlying emotional processing and between fronto-temporal function and striatal dopamine function in cognitive functions impaired in schizophrenia. Treatments targeting these circuits may thus be beneficial.

Winner of the 2014 BAP Senior Clinical Psychopharmacology Award

PW5

SMARTPHONE AND INTERNET-BASED INHIBITORY CONTROL TRAINING FOR PROBLEM DRINKERS

Jones AJ, Box 219 Eleanor Rathbone Bldg, Univ of Liverpool, Bedford Street South, Liverpool L69 7ZA, A.J.Jones@liverpool.ac.uk
Tiplady B, Field M

Introduction: Problematic drinkers are characterised by deficits in inhibitory control, which is the ability to stop, change or delay a behaviour that is no longer appropriate. Evidence suggests that inhibitory control is a state variable, and fluctuations may increase the risk of alcohol use. Given the potential causal relationship, strengthening inhibitory control may be a feasible target of behavioural interventions. Our current research is using novel methods of task administration to capture intra-individual differences and improve inhibitory control in the natural environment. Methods: We have developed a version of the Stop Signal task deliverable via a smartphone application ('app'). In two studies we loaned problem drinkers smartphones and prompted them to complete this app twice-per-day for two weeks. Study one examined daily fluctuations in inhibition and study two examined whether manipulation of task parameters led to improvements in inhibition. Results: Compliance with the apps was high (~94%) and test re-test reliabilities were in line with laboratory research (r=.67). Speed accuracy trade offs (rs>.90) were evident during the tasks suggesting participants were performing the task correctly without supervision. In both studies practicing inhibitory control led to significant improvements over time. Conclusions: Advances in technology present us with new methods of data capture and potential avenues for behavioural training administration. The results of these studies may lead to new approaches to the measurement and treatment of alcohol-related problems that are relatively inexpensive, make minimal demands on healthcare services and can be accessed by the majority of the population.

Winner of the 2014 Junior BAP/Cambridge Cognition Award
Most UK adults (62%) are overweight or obese, costing the NHS over £5 billion a year. Computerised response inhibition training could improve self-control in individuals who overeat. Training people to inhibit simple motor responses (key presses) to specific food pictures reduces the subsequent consumption of those foods by up to 40%. We examined whether different types of response inhibition training modify eating behaviour in the lab and at home. Our first between-subjects lab experiment (N = 65) compared the effects of stop vs. dual (two key-presses) response training to food pictures on immediate consumption of one snack food (crisps). Our second study (N = 170) offered two foods (crisps and chocolate), one of which was not associated with stopping, to enable within- and between-subjects comparisons of intake. We also added a control condition in which participants had to ignore stop signals and respond with one key-press to all pictures. Our third lab experiment (N = 170) compared the effects of stop vs. dual response training to non-food pictures. Finally, we conducted a pilot randomised controlled trial in a community sample (N = 87) to examine whether repeated no-go training to food vs. non-food pictures, delivered via the internet, modified real world eating behaviour. Daily snacking, 24-hour food diaries, food stimulus ratings and weight were measured before and after one week (4 sessions) of no-go training. Our first study showed significant (p < .05) reductions in crisp intake following food-related stop vs. dual response training. Our second study showed no overall effects of training (food-related stop, dual or ‘ignore’ control), but effects were moderated by dietary restraint: Restrained eaters ate less following stop vs. dual, but not vs. control training. Our third experiment showed no effect of general (non-food) stop vs. dual response training. Our pilot RCT suggested significant reductions in weight, food ratings and calorie intake (food diaries), but not self-reported snacking frequency, following repeated food no-go training. These findings suggest some stimulus-specific effects of response inhibition training on food intake that are moderated by dietary restraint. However, lab studies may be confounded by increased food intake in the dual-response comparison groups, consistent with the effects of food cue exposure increasing intake. Nevertheless, our pilot RCT indicates promising effects of food-associated response inhibition training on weight loss. Excellent adherence (94%) to, and positive feedback about the training further suggests it has the potential to reduce overweight and obesity. This work was generously supported by a Wellcome Trust Institutional Strategic Support Award (WT097835MF) Winner of the 2014 Senior BAP/Cambridge Cognition Award
<table>
<thead>
<tr>
<th>Presenting Author</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adams S</td>
<td>A29</td>
</tr>
<tr>
<td>Ainsworth B</td>
<td>A82</td>
</tr>
<tr>
<td>Alford C</td>
<td>A83</td>
</tr>
<tr>
<td>Almatroudi AM</td>
<td>A101</td>
</tr>
<tr>
<td>Anderson IM</td>
<td>A41</td>
</tr>
<tr>
<td>Andrews H</td>
<td>A116</td>
</tr>
<tr>
<td>Arnoue D</td>
<td>A90, A91</td>
</tr>
<tr>
<td>Bailey JC</td>
<td>A87</td>
</tr>
<tr>
<td>Bakunina N</td>
<td>A108</td>
</tr>
<tr>
<td>Bamford S</td>
<td>A41, A61</td>
</tr>
<tr>
<td>Banca P</td>
<td>A26, A116</td>
</tr>
<tr>
<td>Bannerton K</td>
<td>A101</td>
</tr>
<tr>
<td>Barnes TRE</td>
<td>A69</td>
</tr>
<tr>
<td>Barron M</td>
<td>A67</td>
</tr>
<tr>
<td>Beck KE</td>
<td>A51</td>
</tr>
<tr>
<td>Biaggi A</td>
<td>A32</td>
</tr>
<tr>
<td>Blakemore S-J</td>
<td>A8</td>
</tr>
<tr>
<td>Bloomfield MAP</td>
<td>A22, A128</td>
</tr>
<tr>
<td>Bloomfield PS</td>
<td>A114</td>
</tr>
<tr>
<td>Bolea B</td>
<td>A124</td>
</tr>
<tr>
<td>Borsini A</td>
<td>A96</td>
</tr>
<tr>
<td>Braithwaite EC</td>
<td>A96</td>
</tr>
<tr>
<td>Brandish EK</td>
<td>A120</td>
</tr>
<tr>
<td>Brandon NJ</td>
<td>A8</td>
</tr>
<tr>
<td>Brazaitis CT</td>
<td>A12</td>
</tr>
<tr>
<td>Breen G</td>
<td>A8</td>
</tr>
<tr>
<td>Brennand KJ</td>
<td>A7</td>
</tr>
<tr>
<td>Brett RR</td>
<td>A114</td>
</tr>
<tr>
<td>Brown GR</td>
<td>A9</td>
</tr>
<tr>
<td>Browning M</td>
<td>A60</td>
</tr>
<tr>
<td>Bruhl AB</td>
<td>A42</td>
</tr>
<tr>
<td>Bulage GB</td>
<td>A83</td>
</tr>
<tr>
<td>Bullmore ET</td>
<td>A2</td>
</tr>
<tr>
<td>Button KS</td>
<td>A32</td>
</tr>
<tr>
<td>Campbell A</td>
<td>A27</td>
</tr>
<tr>
<td>Campbell-Meiklejohn DK</td>
<td>A76</td>
</tr>
<tr>
<td>Carhart-Harris RL</td>
<td>A82</td>
</tr>
<tr>
<td>Carlisi CO</td>
<td>A125</td>
</tr>
<tr>
<td>Cattaneo A</td>
<td>A126</td>
</tr>
<tr>
<td>Chamberlain S</td>
<td>A4</td>
</tr>
<tr>
<td>Chandrasekera S</td>
<td>A24</td>
</tr>
<tr>
<td>Charpentier CJ</td>
<td>A79</td>
</tr>
<tr>
<td>Cheeta S</td>
<td>A70</td>
</tr>
<tr>
<td>Ciufolini S</td>
<td>A48</td>
</tr>
<tr>
<td>Clark JE</td>
<td>A38, A97, A98</td>
</tr>
<tr>
<td>Clarke HF</td>
<td>A93</td>
</tr>
<tr>
<td>Clifton NE</td>
<td>A110</td>
</tr>
<tr>
<td>Coates J</td>
<td>A55</td>
</tr>
<tr>
<td>Cocks R</td>
<td>A24</td>
</tr>
<tr>
<td>Cortese S</td>
<td>A4</td>
</tr>
<tr>
<td>Costafreda SG</td>
<td>A50</td>
</tr>
<tr>
<td>Cotell MC</td>
<td>A115</td>
</tr>
<tr>
<td>Cousins L</td>
<td>A33</td>
</tr>
<tr>
<td>Curran V</td>
<td>A5</td>
</tr>
<tr>
<td>Dalili MN</td>
<td>A78</td>
</tr>
<tr>
<td>Dalley JW</td>
<td>A11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Presenting Author</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Das RK</td>
<td>A30</td>
</tr>
<tr>
<td>Davies SJC</td>
<td>A100</td>
</tr>
<tr>
<td>Daw ND</td>
<td>A11</td>
</tr>
<tr>
<td>Dawson N</td>
<td>A112</td>
</tr>
<tr>
<td>Deslandes PN</td>
<td>A55</td>
</tr>
<tr>
<td>Di Simplicio M</td>
<td>A127</td>
</tr>
<tr>
<td>Doherty AE</td>
<td>A33</td>
</tr>
<tr>
<td>Du Preez A</td>
<td>A107</td>
</tr>
<tr>
<td>Dutta A</td>
<td>A94</td>
</tr>
<tr>
<td>Eagle DM</td>
<td>A64</td>
</tr>
<tr>
<td>Ebmeier K</td>
<td>A3</td>
</tr>
<tr>
<td>Egeland M</td>
<td>A126</td>
</tr>
<tr>
<td>Ersche KD</td>
<td>A6</td>
</tr>
<tr>
<td>Ettinger U</td>
<td>A75, A128</td>
</tr>
<tr>
<td>Fachim HA</td>
<td>A109</td>
</tr>
<tr>
<td>Fantini E</td>
<td>A96</td>
</tr>
<tr>
<td>Faroq S</td>
<td>A34</td>
</tr>
<tr>
<td>Freeman TP</td>
<td>A19</td>
</tr>
<tr>
<td>Frey AL</td>
<td>A42</td>
</tr>
<tr>
<td>Fu CH</td>
<td>A3</td>
</tr>
<tr>
<td>Fust M</td>
<td>A51</td>
</tr>
<tr>
<td>Gabay AS</td>
<td>A58</td>
</tr>
<tr>
<td>Gage S</td>
<td>A39</td>
</tr>
<tr>
<td>Gillougley C</td>
<td>A111</td>
</tr>
<tr>
<td>Giordano AG</td>
<td>A47</td>
</tr>
<tr>
<td>Godlew ska BR</td>
<td>A45</td>
</tr>
<tr>
<td>Godley A</td>
<td>A16</td>
</tr>
<tr>
<td>Goodyer IM</td>
<td>A9</td>
</tr>
<tr>
<td>Goozey ZY</td>
<td>A87</td>
</tr>
<tr>
<td>Gormley S</td>
<td>A105</td>
</tr>
<tr>
<td>Grabski MG</td>
<td>A80</td>
</tr>
<tr>
<td>Granger KG</td>
<td>A60</td>
</tr>
<tr>
<td>Guiriguis A</td>
<td>A34</td>
</tr>
<tr>
<td>Gurney M</td>
<td>A112</td>
</tr>
<tr>
<td>Hagan CC</td>
<td>A91</td>
</tr>
<tr>
<td>Hales CA</td>
<td>A102</td>
</tr>
<tr>
<td>Harper AJ</td>
<td>A16</td>
</tr>
<tr>
<td>Harrison L</td>
<td>A70</td>
</tr>
<tr>
<td>Harun N</td>
<td>A88</td>
</tr>
<tr>
<td>Hayward A</td>
<td>A122</td>
</tr>
<tr>
<td>Hazekamp A</td>
<td>A5</td>
</tr>
<tr>
<td>Hazelgrove K</td>
<td>A49</td>
</tr>
<tr>
<td>Hepgul N</td>
<td>A99</td>
</tr>
<tr>
<td>Herane Vives A</td>
<td>A98</td>
</tr>
<tr>
<td>Hindocha C</td>
<td>A59</td>
</tr>
<tr>
<td>Holmes SE</td>
<td>A47</td>
</tr>
<tr>
<td>Hong E</td>
<td>A10</td>
</tr>
<tr>
<td>Horndasch S</td>
<td>A72</td>
</tr>
<tr>
<td>Horowitz MA</td>
<td>A105</td>
</tr>
<tr>
<td>Hou R</td>
<td>A118</td>
</tr>
<tr>
<td>Howard M</td>
<td>A73</td>
</tr>
<tr>
<td>Howells HG</td>
<td>A35</td>
</tr>
<tr>
<td>Howes O</td>
<td>A129</td>
</tr>
<tr>
<td>Huxter JR</td>
<td>A17</td>
</tr>
<tr>
<td>Iqbal S</td>
<td>A43</td>
</tr>
<tr>
<td>Ironside M</td>
<td>A61</td>
</tr>
<tr>
<td>Presenting Author</td>
<td>Page</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Isherwood SN</td>
<td>A13, A122</td>
</tr>
<tr>
<td>Jackson SAW</td>
<td>A15</td>
</tr>
<tr>
<td>Jedras P</td>
<td>A80</td>
</tr>
<tr>
<td>Jenkins TA</td>
<td>A113</td>
</tr>
<tr>
<td>Jennings EM</td>
<td>A71</td>
</tr>
<tr>
<td>Jones AJ</td>
<td>A129</td>
</tr>
<tr>
<td>Jones BDM</td>
<td>A97</td>
</tr>
<tr>
<td>Juhasz G</td>
<td>A39</td>
</tr>
<tr>
<td>Jupp B</td>
<td>A125</td>
</tr>
<tr>
<td>Kaelen M</td>
<td>A43</td>
</tr>
<tr>
<td>Kaser M</td>
<td>A84</td>
</tr>
<tr>
<td>Katzman D</td>
<td>A8</td>
</tr>
<tr>
<td>Khandaker GM</td>
<td>A40</td>
</tr>
<tr>
<td>Kilford EJ</td>
<td>A76</td>
</tr>
<tr>
<td>Kim CH</td>
<td>A17</td>
</tr>
<tr>
<td>Kokkinou M</td>
<td>A21, A115</td>
</tr>
<tr>
<td>Kotoula V</td>
<td>A78</td>
</tr>
<tr>
<td>Kwong ASF</td>
<td>A62</td>
</tr>
<tr>
<td>Lau JYN</td>
<td>A65</td>
</tr>
<tr>
<td>Lawn W</td>
<td>A29</td>
</tr>
<tr>
<td>Lawrence NS</td>
<td>A74, A130</td>
</tr>
<tr>
<td>Lawrie S</td>
<td>A7</td>
</tr>
<tr>
<td>Leger M</td>
<td>A111</td>
</tr>
<tr>
<td>Leyton M</td>
<td>A7</td>
</tr>
<tr>
<td>Li j</td>
<td>A106</td>
</tr>
<tr>
<td>Limbrick-Oldfield EH</td>
<td>A23</td>
</tr>
<tr>
<td>Lovestone S</td>
<td>A1</td>
</tr>
<tr>
<td>Lythe KE</td>
<td>A95</td>
</tr>
<tr>
<td>Malik NN</td>
<td>A16</td>
</tr>
<tr>
<td>Mansvelder H</td>
<td>A9</td>
</tr>
<tr>
<td>Marino M</td>
<td>A49</td>
</tr>
<tr>
<td>McCabe C</td>
<td>A73</td>
</tr>
<tr>
<td>McDonnell-Dowling K</td>
<td>A88</td>
</tr>
<tr>
<td>McFarquhar M</td>
<td>A44</td>
</tr>
<tr>
<td>McGrath E</td>
<td>A80</td>
</tr>
<tr>
<td>McShane R</td>
<td>A36</td>
</tr>
<tr>
<td>Mechelmans DJ</td>
<td>A31</td>
</tr>
<tr>
<td>Mercuri K</td>
<td>A81</td>
</tr>
<tr>
<td>Meron D</td>
<td>A36</td>
</tr>
<tr>
<td>Michaud DR</td>
<td>A84</td>
</tr>
<tr>
<td>Mick I</td>
<td>A25</td>
</tr>
<tr>
<td>Mitchell SH</td>
<td>A85</td>
</tr>
<tr>
<td>Mokrysz C</td>
<td>A20</td>
</tr>
<tr>
<td>Mondelli V</td>
<td>A50</td>
</tr>
<tr>
<td>Morein-Zamir S</td>
<td>A117</td>
</tr>
<tr>
<td>Moreira FA</td>
<td>A89</td>
</tr>
<tr>
<td>Morris LS</td>
<td>A72</td>
</tr>
<tr>
<td>Morrison P</td>
<td>A5</td>
</tr>
<tr>
<td>Moss A</td>
<td>A30</td>
</tr>
<tr>
<td>Mouchliantis E</td>
<td>A52</td>
</tr>
<tr>
<td>Murphy A</td>
<td>A27</td>
</tr>
<tr>
<td>Murphy SE</td>
<td>A92</td>
</tr>
<tr>
<td>Musaelyan K</td>
<td>A102</td>
</tr>
<tr>
<td>Muthukumaraswamy SD</td>
<td>A93</td>
</tr>
<tr>
<td>Myers JFM</td>
<td>A63</td>
</tr>
<tr>
<td>Presenting Author</td>
<td>Page</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Sykes LLH</td>
<td>A110</td>
</tr>
<tr>
<td>Symonds CS</td>
<td>A77, A95</td>
</tr>
<tr>
<td>Taylor EM</td>
<td>A21</td>
</tr>
<tr>
<td>Tedford SE</td>
<td>A66</td>
</tr>
<tr>
<td>Thomas JM</td>
<td>A72</td>
</tr>
<tr>
<td>Tobias-Webb J</td>
<td>A79</td>
</tr>
<tr>
<td>Tojo LM</td>
<td>A108</td>
</tr>
<tr>
<td>Tolomeo ST</td>
<td>A26, A90</td>
</tr>
<tr>
<td>Tomassi S</td>
<td>A48</td>
</tr>
<tr>
<td>Tomlinson A</td>
<td>A123</td>
</tr>
<tr>
<td>Treasure J</td>
<td>A4</td>
</tr>
<tr>
<td>Trent S</td>
<td>A18</td>
</tr>
<tr>
<td>Vaghi MMS</td>
<td>A118</td>
</tr>
<tr>
<td>Valton V</td>
<td>A58</td>
</tr>
<tr>
<td>van de Loo AJAE</td>
<td>A19</td>
</tr>
<tr>
<td>van der Flier FE</td>
<td>A117</td>
</tr>
<tr>
<td>Vernon AC</td>
<td>A104</td>
</tr>
<tr>
<td>Verster JC</td>
<td>A19</td>
</tr>
<tr>
<td>Voon V</td>
<td>A12</td>
</tr>
<tr>
<td>Wallace J</td>
<td>A68</td>
</tr>
<tr>
<td>Wallis C</td>
<td>A104</td>
</tr>
<tr>
<td>Warren MB</td>
<td>A62</td>
</tr>
<tr>
<td>Watremez W</td>
<td>A68</td>
</tr>
<tr>
<td>Watson S</td>
<td>A38</td>
</tr>
<tr>
<td>Wehmann E</td>
<td>A69</td>
</tr>
<tr>
<td>Wellman P</td>
<td>A84</td>
</tr>
<tr>
<td>Wickens RA</td>
<td>A107</td>
</tr>
<tr>
<td>Williams MR</td>
<td>A46</td>
</tr>
<tr>
<td>Wilson SJ</td>
<td>“A64, A70”</td>
</tr>
<tr>
<td>Wing VC</td>
<td>“A10, A23”</td>
</tr>
<tr>
<td>Wing VC</td>
<td>A23</td>
</tr>
<tr>
<td>Wise T</td>
<td>A92</td>
</tr>
<tr>
<td>Wood CM</td>
<td>A14</td>
</tr>
<tr>
<td>Wright VL</td>
<td>A85</td>
</tr>
<tr>
<td>Young JW</td>
<td>A14</td>
</tr>
<tr>
<td>Zajkowska Z</td>
<td>A99</td>
</tr>
</tbody>
</table>