JOURNAL OF PSYCHOPHARMACOLOGY

SUPPLEMENT TO ISSUE 31, NUMBER 8, AUGUST 2017

These papers were presented at the Summer Meeting of the

BRITISH ASSOCIATION FOR PSYCHOPHARMACOLOGY

23 – 26 July, Harrogate, 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 2017

Abstracts begin on page:

POSTERS

POSTDOCTORAL SYMPOSIUM

SHORT ORAL PRESENTATIONS

S01

WILL A GENETIC TEST HELP SELECT TREATMENT FOR INDIVIDUALS WITH DEPRESSION?

Uher R, Dept of Psychiatry, Dalhousie University, Abbie J. Lane Bldg, room 4082, 5909 Veterans' Memorial Lane, Halifax, Nova Scotia, Canada, B3H 2E2 uher@dal.ca

Outcomes of major depressive disorder (MDD) could be improved if treatment choice is informed by genetic data. Genetic test would be valuable since it only needs to be carried out once in individual's life-time and provides high accuracy measurement at moderate cost. Genetic tests could help decide between different types of antidepressant medication or help personalize indications for different treatment modalities, including psychological treatment and neurostimulation. Several large-scale studies have tested the hypothesis that a single common genetic variant exists that could predict response to antidepressants in a clinically meaningful way, but have identified no such variant. It is estimated that between a third and a half of variance in whether individuals respond to common antidepressant treatments could be explained by a large number of common genetic variants of individually small effects. Current efforts are directed towards the integration of multiple genetic and clinical predictors to obtain a reproducible and clinically meaningful prediction of who is likely to respond to which treatment. Recent data collection includes a broad array of clinical variables and brain measurement in addition to genetic and transcriptomic data in individuals treated with antidepressants with and without augmentation, cognitive-behavioral therapy and transcranial magnetic stimulation. The presenter will critically discuss the promise and challenges of such multimodal approaches. The work leading to this presentation has been completed thanks to funding from the Canada Research Chairs Program, the Canadian Institutes of Health Research (Grant reference numbers 124976, 142738 and 148394), European Commission, Nova Scotia Health Research Foundation, Ontario Brain Institute and the Dalhousie Medical Research Foundation.

S02

INFLAMMATION AND THE BRAIN IN DEPRESSION: CAN INFLAMMATION INFORM TREATMENT CHOICES?

Harrison NA, Brighton and Sussex Medical School, University of Sussex, Clinical Imaging Sciences Centre University of Sussex Brighton, BN1 9RR n.harrison@bsms.ac.uk

Inflammation is increasingly implicated in the aetiology of depression. Patients with depression have elevated pro-inflammatory markers, particularly IL-6 and CRP and large-scale transcriptomics implicate NF-κB and type-I Interferon signalling pathways. Furthermore, recent studies have linked raised inflammatory markers to impaired response to classical anti-depressants while small-scale trials of 'anti-inflammatory' agents have suggested anti-depressant efficacy in patients with raised inflammatory markers. In this talk I shall review evidence for a 'pro-inflammatory' profile in patients with depression and discuss current evidence for how this may help inform anti-depressant treatment choice. No sponsorship was received for this study.

S03

MRI AND COGNITIVE BIOMARKERS IN PREDICTION OF ANTIDEPRESSANT RESPONSE: BIG DATA STUDIES

Godlewska B, Dept of Psychiatry, Univ of Oxford, Warneford Lane, Oxford, OX3 7EQ beata.godlewska@psych.ox.ac.uk

Predicting treatment response in major depressive disorder would mean a major breakthrough in treatment delivery. Current treatment attempts are still 'trial and error', with less than 50% of patients responding to their first treatment, and weeks or months passing until response is achieved. Being able to make a choice of an effective treatment before it is started would mean a tremendous decrease in the burden at both individual and societal level. Of the areas explored in this search, cognitive and MRI biomarkers have provided some promising findings. Over the past two decades MRI related techniques have been increasingly employed in the search for biological markers of treatment response. This is linked to a relatively quick development of technologies, which provide more accurate and detailed information

about the structure and function of specific regions of the brain. This allows more precision in exploring the links between processes in the brain and treatment outcomes. Extensive research has led to an identification of regions of the brain which activity differentiated between responders and non responders to various treatments, such as the pregenual or subgenual ACC or the amygdala. The development of other techniques, such as MRS at high field strengths, allows a better understanding of baseline biological processes, at the level of neurotransmitters, and an exploration of their relationship with treatment response. Cognitive biomarkers may be simpler to assess and hence more useful at the practical level than MRI related ones. However, despite promising and consistently replicated findings at group levels, at this point no single cognitive or MRI marker has shown sufficient power to allow reliable matching of an individual to an effective treatment and none can be used in standard clinical practice. The next important step is big data approach, involving an exploration of multiple markers, their combinations, and testing hypotheses on large numbers of patients in large collaborative studies. In this talk I will review the current state of knowledge regarding MRI and cognitive biomarkers of differential response to various forms of treatment, such as pharmacotherapy, tDCS, and psychotherapy. I will talk about studies conducted by our group, and big collaborative efforts such as ENIGMA and EMBARC projects.

S04

USING MACHINE LEARNING AND CLINICAL VARIABLES TO PREDICT ANTIDEPRESSANT RESPONSE

Browning M, Psychiatry, University of Oxford and P1vital Ltd, Neuroscience Building, Warneford Hospital, Oxford, OX3 7JX michael.browning@psych.ox.ac.uk

Background Antidepressants have a slow clinical onset of action and patients will often not respond to the initial medications prescribed. No test exists to guide clinicians as to whether their patient is responding or not. This often results in delays of many months before patients are initiated on effective treatment. The PReDicT (Predicting Response to Depression Treatment) test is a computer-based task which measures antidepressant induced change in the processing of emotional information as well as symptoms of depression. It has been designed to predict, early in the course of antidepressant treatment, whether a patient will respond to that treatment. In this talk I will describe initial studies during which the test performance of the PReDicT test was established as well as an ongoing multi-site RCT which is assessing the impact of using the PReDicT test to guide antidepressant treatment in primary care. Methods A pilot study of 57 primary care patients with depression from the UK was completed to establish predictive test performance. The PReDicT test was completed at baseline and after 1 week of treatment. All patients were treated with citalopram and response was defined as a greater than 50% reduction of baseline QIDS score by week 4-6. A multi-centre randomised controlled trial (the PReDicT trial) is currently underway across Europe. In this study primary care patients with depression are randomised to have their treatment guided by the PReDicT test vs. treatment as usual. The primary outcome is QIDS response at week 8. Study recruitment is ongoing. Results Response rates in the studies ranged from 39-54%. Across studies, the accuracy of the PReDicT test is 10-20% higher than can be achieved using these baseline rates. Discussion These results demonstrate that measures of the induced change in cognitive and symptom based measures provide predictive information about antidepressant response. The real world clinical benefit of this information is currently being assessed in a large scale trial. CoI: I am employed for 0.5 days/week by P1vital who own the PReDicT test and who sponsored and funded the above studies.

S05

VOLTAGE GATED CALCIUM CHANNELS: A REVIEW OF NEURONAL FUNCTION AND DYSFUNCTION

Dolphin AC, Dept of Neuroscience, Physiology and Pharmacology, University College London, Andrew Huxley Building, Gower St, London, WC1E 6BT a.dolphin@ucl.ac.uk

Ca2+ entry into cells via voltage gated Ca2+ channels is an important contributor to Ca2+ signaling in excitable cells, and these channels are essential to the function of neuronal circuits. The voltage-gated calcium channels consist of three main subunits, the α1 pore-forming subunit, the intracellular β and extracellular α2δ. There are 10 mammalian α1 subunit genes, divided into three classes (CaV1 – CaV3). The CaV1 and CaV2 classes are associated with the auxiliary β and α2δ subunits, of which there are four

genes each. A number of mutations have been described in calcium channel genes that are associated with rare diseases, and also single nucleotide polymorphisms that have been linked to more common diseases, at a population level. The CACNA1C gene, encoding an “L-type” channel, CaV1.2, is mutated in a rare disease called Timothy syndrome, which is a multisystem disorder associated with cardiac arrhythmias, syndactyly, cognitive impairment and autism symptoms. All mutations so far identified are gain of function, and many of them are in exon 8, or the alternatively spliced exon 8A. The CACNA1D gene encoding CaV1.3, also exhibits mutations that have been linked to autism and cognitive impairment, as well as resistant hypertension. Furthermore, somatic gain-of-function mutations in this gene result in the development of aldosterone-secreting adenomas in the zona glomerulosa of the adrenal cortex, and some of these mutations are in the equivalent alternative exons 8A and 8B, which form a hotspot for gain-of function mutations. These somatic mutations are increasingly diagnosed as a cause of drug-resistant hypertension. The calcium channel gene superfamily have also been connected to multiple neuropsychiatric disorders, including bipolar disorder, schizophrenia, autism spectrum disorders and intellectual impairment. It is more difficult to demonstrate whether and how a functional link occurs between the mutations identified in whole exome sequencing, or the single nucleotide polymorphisms identified in Genome Wide Association Studies, and the neuropsychiatric disease processes. A major challenge for the future will be to determine what potential these findings provide for patient treatment. In my talk I will describe the basic properties, distribution and function of these voltage-gated calcium channels, to provide a basis for understanding their potential role in neuropsychiatric disease.

S06

A SYSTEMATIC REVIEW OF CALCIUM CHANNEL ANTAGONISTS IN BIPOLAR DISORDER, AND THEIR FUTURE POTENTIAL

Cipriani A, Department of Psychiatry, University of Oxford, Warneford Hospital Oxford UK, OX3 7JX andrea.cipriani@psych.ox.ac.uk

Saunders K(1), Geddes JR(1), Tunbridge EM(2), Harrison PJ(2)

(1) Univ Dept of Psychiatry, Warneford Hosp, Oxford OX3 7JX; (2) Neurosciences Bldg, Univ Dept of Psychiatry, Warneford Hosp, Oxford OX3 7JX

Introduction L-type calcium channel (LTCC) antagonists have been used in bipolar disorder for over 30 years, without becoming an established therapeutic approach. Interest in this class of drugs has been rekindled by the discovery that LTCC genes are part of the genetic aetiology of bipolar disorder. We have therefore conducted a systematic review of LTCC antagonists in the treatment and prophylaxis of bipolar disorder. Methods We searched the following electronic databases up to February 2016: the Cochrane Library, Medline, EMBASE, CDSR, DARE, HTA, CINAHL and PsycINFO. International trial registries were searched for unpublished data. No restrictions on language was applied. At least two researchers independently identified eligible studies. Results We identified 23 eligible studies, with six randomised, double-blind, controlled trials, all investigating verapamil in acute mania (81 patients assigned to verapamil and 76 received another compound: placebo = 22, lithium = 54). Verapamil was not superior to placebo (Standardised Mean Difference [SMD] - 0.39, 95% CI - 1.38 to 0.59) and lithium was not statistically significantly better than verapamil (SMD 0.17, 95% CI - 0.30 to 0.65). One study recruited only lithium-resistant patients and found no difference between lithium and verapamil as response rate (4 out of 8 responded to lithium versus 3 out of 10 to verapamil; risk ratio (RR) 0.60, 95% CI 0.19 to 1.94). In terms of acceptability, placebo resulted with more patients terminating the study (6 out of 15 versus 3 out of 17; RR 2.27, 0.68 to 7.52), however the difference was not statistically significant. No controlled data were identified for LTCC antagonists in the prophylaxis of bipolar disorder, nor for bipolar depression. We found 17 observational studies that were included for consideration of adverse events only: two non-randomised double-blind trials, seven open label studies and eight case reports. Verapamil was the most frequently used LTCC antagonist (N=11) with two studies using diltiazem, and single studies using nimodipine, nifedipine, methyoxyverapamil or isradipine. Adverse events were poorly reported across all study types, with the commonly reported side effects being all related to the peripheral actions of LTCC antagonists and being predominantly cardiovascular in nature. Conclusions LTCC antagonists have been

tested neither carefully nor optimally in clinical trials, and hence it is still uncertain whether they have a role in the treatment of depressive or manic episodes, or in maintenance. Given the increasingly strong evidence for calcium signalling dysfunction in bipolar disorder, the therapeutic candidacy of this class of drugs has become stronger. In particular, genetic, molecular and pharmacological data can be used to improve the selectivity, efficacy and tolerability of LTCC antagonists. The development of 'brain-selective' LTCC ligands could be one fruitful approach to innovative pharmacotherapy for bipolar disorder. Funding: This research was supported by a Wellcome Trust Strategic Award (CONBRIO: Collaborative Network for Bipolar Research to Improve Outcomes) and by the NIHR Oxford cognitive health Clinical Research Facility.

S07

TRANSLATIONAL STUDIES OF THE PHENOTYPIC EFFECTS OF GENETIC VARIATION IN THE PSYCHIATRIC RISK GENE CACNA1C

Hall J, Neuroscience and Mental Health Research Institute, Cardiff University, Hadyn Ellis Building Maindy Road, CF24 4HQ hallj10@cardiff.ac.uk

Genetic studies have identified variation in the gene CACNA1C associated with a number of psychiatric disorders including schizophrenia, bipolar disorder and autism. CACNA1C encodes the alpha1C subunit of the Cav1.2 L-Type voltage gated calcium channel. In order to characterise the effects of variation in this gene on risk for neuropsychiatric disorders more fully we have undertaken translational studies using pharmacological approaches and a novel transgenic rat model (hemizygous deletion of Cacna1c) and in human risk allele carriers. We have focussed on measures of associative learning and reversal learning. Our findings include a selective effect of genetic variation in CACNA1C on forms of inhibitory learning, including latent inhibition, and on reversal learning - an effect also seen in human risk allele carriers. These results will be discussed in relation to the development of models for testing and developing drugs targeting L-Type VGCCs for use in neuropsychiatric disorders.

S08

TOWARDS BRAIN SELECTIVE CALCIUM CHANNEL ANTAGONISTS FOR PSYCHIATRY

Tunbridge EM, Department of Psychiatry, University of Oxford, Neurosciences Bldg Univ Dept Psychiatry Warneford Hospital, OX37JX elizabeth.tunbridge@psych.ox.ac.uk

Recent genomic findings have spurred interest in voltage gated calcium channels (VGCCs) as potential therapeutic targets for psychiatric disorders. VGCCs are expressed widely and play important roles throughout the body; indeed, calcium channel blockers are already licensed for cardiovascular indications including hypertension and angina. However, their ubiquitous expression raises the potential for off-target effects of VGCC-targeting drugs intended for the treatment of psychiatric disorders. This presentation will consider how we might more selectively target VGCCs relevant for brain function. The development of brain-selective VGCC agents is limited by a lack of information about the specific receptor isoforms that are present in human brain. This information is critical, since VGCC subunit genes are large and complex. VGCC subunit genes typically give rise to multiple splice isoforms, which differ significantly in their functional properties. I will present data on the human brain splicing profile of the VGCC gene showing the strongest genetic association with psychiatric disorders: the CACNA1C gene. Our findings demonstrate the presence of a number of novel CACNA1C exons and transcripts in human brain, which may ultimately encode more selective therapeutic targets for psychiatric disorders. Sponsorship: Royal Society; MRC.

S09

CROSS-CUTTING DIAGNOSTIC AND NEUROBIOLOGICAL ISSUES IN BEHAVIOURAL ADDICTIONS: A VALID CONCEPT?

Chamberlain SR, Department of Psychiatry, University of Cambridge, Box 189, Level E4, Addenbrookes Hospital, Cambridge., CB20QQ src33@cam.ac.uk

Introduction: The concept of 'behavioural addiction' draws analogies with substance addiction. Proponents of the behavioural addiction model argue that, as certain substances have high abuse liability, so too are certain behaviours intrinsically rewarding and prone to repetition. Opponents of this model suggest that

other approaches may be more valuable, such as considering conditions as being obsessive-compulsive (characterized by rigid or stereotyped thoughts/behaviours), or impulsive (characterized by behaviours that are unduly hasty, not well thought through, or risky). However repetitive behavioural disorders are defined, they merit clinical and research scrutiny due to their high prevalence and untoward functional consequences. Methods: Selective overview of cross-cutting diagnostic and neurobiological issues in behavioural addiction research. Results: Behaviours highlighted as potentially addictive in the extant literature include gambling, shopping, sex, stealing, grooming (hair pulling, skin picking), and Internet use. The Diagnostic and Statistical Manual (DSM-5) saw the creation of a new category of "Substance-Related and Addictive Disorders", which includes gambling disorder. In contrast, the Working Group on Obsessive-Compulsive Disorders for the International Classification of Diseases (ICD-11) recommended retaining a category of "impulse control disorders" to include gambling, stealing, and compulsive sexual behaviour. Both nosological approaches regard hair-pulling and skin-picking as obsessive-compulsive related disorders, and do not formally recognize compulsive buying/shopping or Internet use disorders. Conclusions: Mixed data are found to support the conceptualization of different disorders as behavioural addictions, versus as obsessive-compulsive disorders, or impulse control disorders. Evidence to date supports a strong relationship between gambling disorder and substance use disorders. While grooming disorders are regarded by both DSM-5 and (likely) by ICD-11 as obsessive-compulsive disorders, their neurocognitive and imaging profiles differ considerable from obsessive-compulsive disorder. It is suggesting that Internet addiction merits consideration as a formal disorder, based on findings of its functional consequences, prevalence, and neurobiology. Translational approaches focusing on top down control, reward processing, and flexible responding appear particularly helpful in furthering optimal diagnosis and treatment of these repetitive disorders. Intermediate markers of impulsivity and compulsivity show promise in this context, incorporating measures not only of behaviour but also of personality and cognitive functioning. This transdiagnostic method is exemplified by showing as yet unpublished data from a population cohort. Funding: Wellcome Trust Fellowship (110049/Z/15/Z).

S10

NEUROIMAGING AND COGNITION OF GAMBLING COMPARED WITH SUBSTANCE ADDICTION

Goudriaan AE, Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam Institute for Addiction Research P.O. Box 22660, 1100 DD Amsterdam a.e.goudriaan@amc.uva.nl

vanHolst RJ(1), vanTimmeren T(1)

(1) As presenting author

Introduction: In the past decade, neurobiological research on pathological gambling has flourished. Based on neurobiological similarities between pathological gambling and substance use disorders, besides similarities in genetics, diagnostic criteria, and effective treatments, pathological gambling was the first behavioral addiction to be included in the DSM-5 within the revised category Substance-related and addictive disorders. Methods and results: In this presentation, an overview will be given on neurocognitive and neuroimaging findings in pathological gambling, compared to substance use disorders. Similarities and differences in findings between pathological gambling and substance dependence are discussed. Besides similarities involving deficits in executive functions (impulsivity; decision making), also unique neurobiological findings in pathological gambling, relating to specific aspects of gambling that differ from substance use, are considered. Conclusions: Both similarities and differences in neurocognitive and neuroimaging studies of pathological gambling are present, when compared to substance use disorders. Implications of these neurobiological findings for novel intervention research, such as in neuro-modulation studies and personalized medicine are highlighted. AEG is funded by an innovative grant fellowship of the Dutch Scientific Society - Health (NWO-ZonMw).

S11

COMPULSIVE SHOPPING, STEALING, AND INTERNET USE: WHAT DO WE KNOW? WHAT DON'T WE KNOW?

Odlaug BL, H. Lundbeck A/S; Faculty of Health and Medical Sciences, University of Copenhagen, H. Lundbeck A/S Ottiliavej 9 2500 Valby Denmark, 2500 brod@sund.ku.dk

Compulsive buying, stealing (or "kleptomania"), and Internet use comprise three similar yet disparate psychiatric conditions. Each is associated with significant psychosocial and personal consequences, often inducing shame, embarrassment, and social isolation. While compulsive buying and kleptomania have a storied and well-documented literary foundation dating back over 100 years, only recently has the media and academia begun to recognize the deleterious impact these disorders and compulsive Internet use may have on individual health and well-being. What is known about these disorders from a psychiatric perspective, however, is far less than what is unknown at the present time. The unknown nature of these conditions is validated by the fact that only one – kleptomania – has been formally recognized in professional diagnostic criteria, categorized in the "Disruptive, Impulse-control, and Conduct Disorders" section of the DSM-5. However, and while large scale epidemiological studies are lacking, relatively small-scale examinations of sub-populations indicate that each of these disorders is common in the general population, with higher prevalence rates noted in clinical samples: kleptomania: 0.4-9%; compulsive buying: 1-11%; compulsive Internet use: 1-5%. Further, and while research has helped to illuminate the neurobiological and neurocognitive profiles of each of these conditions, endophenotypic markers and the etiology of each of these conditions are absent from our knowledge base at present. It appears, however, that each of these conditions in their pathologic state shares similarities to other behavioural and substance addictions and obsessive-compulsive disorder as illustrated through clinical presentation and overlap (e.g., comorbidities) and data from functional and structural imaging studies. Gaining a better understanding of these conditions is both prudent and timely. Given the atmospheric rise of the Internet over the past 20 years and nearly exponential expansion of access to so-called "smart" technologies worldwide, how individuals interact in cyberspace and how unfettered access impacts the individual (and in particular the developing adolescent brain) is becoming an area of increasing interest to mental and public health professionals. Access to online content and goods poses concerns for both compulsive Internet use and compulsive buying although the short- and long-term impact on both are areas is unknown and in urgent need of examination. With this and further research, one can hope to identify potentially safe and efficacious psychological and pharmacologic treatments for compulsive buying, kleptomania, and compulsive Internet use and subsequently decrease their burden on the individual and society. Financial disclosures: None to report.

S12

EVIDENCE-BASED AND EMERGING TREATMENTS FOR BEHAVIOURAL AND SUBSTANCE ADDICTIONS

Grant J, Dept of Psychiatry & Behavioural Neuroscience, Univ of Chicago, 5841 S. Maryland Ave Chicago, MC3077, USA jongrant@uchicago.edu

Behavioural and substance addictions represent significant public health concerns and are associated with high rates of psychiatric comorbidity and mortality. In addition, addictive behaviours can prove particularly challenging in day-to-day practice, and clinicians can feel unsure of how to treat them. Although research on behavioral addiction is still in an early stage, recent advances in our understanding of motivation and reward have provided substantial insight into the common clinical presentation, neurocognition, and possible shared pathophysiology of these disorders. Because of these advances in clinical and neuroscience research, there is a growing body of evidence-based treatments for addictive disorders, as well as novel targets for developing treatment approaches. This talk will discuss how understanding these elements may provide for common psychological and pharmacological approaches to individuals with these disabling conditions and will suggest ongoing challenges for the future. This work was supported by research grants from NIDA and Forest Pharmaceuticals.

S13

CAUSAL EFFECTS OF CANNABIS USE ON PSYCHOSIS: EVIDENCE FROM MENDELIAN RANDOMISATION ANALYSES

Munafo MR, Experimental Psychology, University of Bristol, 12a Priory Road Bristol, BS8 1TU marcus.munafo@bristol.ac.uk

Burgess S(1), Gage SH(2), Taylor AE(3), Jones HJ(4), Bowden J(4), Davey Smith G(4), Zammit S(4)

(1) Department of Public Health and Primary Care, University of Cambridge; (2) Institute of Psychology Health and Society, University of Liverpool; (3) School of Experimental Psychology, University of Bristol; (4) School of Social and Community Medicine, University of Bristol

Observational associations between cannabis and schizophrenia are well documented, but ascertaining causation is more challenging, due to well-known problems of confounding and reverse causality. Mendelian randomization is a method that uses genetic variants as proxies for an exposure, instead of directly measuring exposure levels, in order to gain an unbiased estimate of the effect of various exposures on health outcomes. We applied bi-directional two-sample Mendelian randomisation analyses to summary-level genome-wide data from the International Cannabis Consortium (ICC) and the Psychiatric Genomics Consortium (PGC2). Single nucleotide polymorphisms (SNPs) associated with cannabis initiation ($P < 10\text{-}5$) and schizophrenia ($P < 5 \times 10\text{-}8$) were combined using an inverse-variance-weighted fixed-effects approach. We also used height and education genome-wide association study data in negative and positive control analyses. There was some evidence consistent with a causal effect of cannabis initiation on risk of schizophrenia [odds ratio (OR) 1.04 per doubling odds of cannabis initiation, 95% confidence interval (CI) 1.01 to 1.07, P = 0.019]. There was strong evidence consistent with a causal effect of schizophrenia risk on likelihood of cannabis initiation (OR 1.10 per doubling of the odds of schizophrenia, 95% CI 1.05 to 1.14, $P = 2.64 \times 10\text{-}5$). Findings were as predicted for the negative control (height: OR 1.00, 95% CI 0.99 to 1.01, P = 0.90) but weaker than predicted for the positive control (years in education: OR 0.99, 95% CI 0.97 to 1.00, P = 0.066) analyses. We also performed two-sample bi-directional Mendelian randomisation using summary-level genome-wide data from the Tobacco And Genetics Consortium and PGC2. Variants associated with smoking initiation and schizophrenia were combined using an inverse-variance-weighted fixed-effects approach. We found evidence consistent with a causal effect of smoking initiation on schizophrenia risk (OR 1.73, 95% CI 1.30 to 2.25, $P < 0.001$). However, after relaxing the P-value threshold, to include variants from more than one gene and minimize the potential impact of pleiotropy, the association was attenuated (OR 1.03, 95% CI 0.97 to 1.09, $P = 0.32$). There was little evidence in support of a causal effect of schizophrenia on smoking initiation (OR 1.01, 95% CI 0.98 to 1.04, $P = 0.32$). MR Egger regression sensitivity analysis indicated no evidence for pleiotropy in the effect of schizophrenia on smoking initiation (intercept OR 1.01, 95% CI 0.99 to 1.02, $P = 0.49$). Our results provide some evidence that cannabis initiation increases the risk of schizophrenia, although the size of the causal estimate is small. We find stronger evidence that schizophrenia risk predicts cannabis initiation. Our findings provide little evidence of a causal association between smoking initiation and schizophrenia, in either direction. However, we cannot rule out a causal effect of smoking on schizophrenia related to heavier, lifetime exposure, rather than initiation.

S14

ASSOCIATION BETWEEN POLYGENIC RISK SCORES, LEVEL OF CANNABIS USE AND RISK OF PSYCHOSIS

DiForti M, SGDP, IoPPN,KCL, De Crespigny Park, SE5 8AF marta.diforti@kcl.ac.uk

Ferraro L(1), LaCascia C(1), Morgan C(2), Murray MR(3), Quattrone D(4), Wu B(4), Lewis C(4)

(1) Dept of Psychiatry and Psychology, Palermo Medical School; (2) Dept of Social Psychiatry, IoPPN,KCL; (3) Psychosis Studies, IoPPN, KCL ; (4) SGDP, IoPPN, KCL

Cannabis use remains the most widely used recreational drug worldwide. In the USA several states have legalised its used and in some for medicinal use. Nevertheless, a significant amount of Epidemiological and experimental study have reported that cannabis use, especially frequent use of high potency varieties increases the risk of psychosis (Di Forti et al, Lancet Psychiatry 2015 Mar;2(3):233-8). Therefore, it becomes

a research priority to identify those individual at greatest risk to develop psychosis following cannabis use. Methods: Using the GWAS and cannabis use data from a large first episode case-control study (N=2300), we aim 1) to estimate the proportion of new cases of psychosis attributable to frequent use and use of High Potency cannabis in 5 EU countries; 2) to test if those with high Polygenic Risk Scores for Psychosis (PRS) for psychosis are also more likely to smoke cannabis and with high frequency; 3) use PRS to test if genetic load for psychosis increases the individual vulnerability to the psychotogenic effects of cannabis. Results: In those EU countries were high potency cannabis is available, the proportion of new cases of Psychosis attributable to its use was between 20% and 37%. Subjects with a PRS for schizophrenia in the highest quartile had a significant increase in the odds to suffer from a psychotic disorder (Adj OR=6.0; 95% CI 3.46-14.25). Regular, users of high potency cannabis did not differ on PRS profiles from occasional users or never users (Pearson chi2(3) = 5.6001 Pr = 0.133). We did not find a significant interaction between PRS X cannabis use in influencing risk to Psychosis. Conclusions: A reduction in use of high potency type of cannabis could lead to a significant reduction in the proportion of new cases of psychosis across Europe.Summuary scores, such as PRS for Schizophrenia, do not explain individual susceptibility to the psychotogenic effects of cannabis. More research is needed to investigate the role of genes mapping at biological plausible pathways. Funding: MRC and European Community's Seventh Framework Program grant (agreement No. HEALTH-F2-2009-241909 [Project EU-GEI]).

S15

EARLY CANNABIS USE, POLYGENIC RISK SCORE FOR SCHIZOPHRENIA AND BRAIN MATURATION IN ADOLESCENCE

Robert G, Psychiatry, University of Rennes, Pôle Hospitalo Universitaire de Psychiatrie Adulte 108 A venue du Général Leclerc Rennes France, 35000 gabriel.hadrien.robert@gmail.com

GunterSchumann GS(1)

(1) Social Genetic and Developmental Psychiatry Institute of Psychiatry, Psychology and Neuroscience, King's College London, SE5 8AF, London

Introduction : Early cannabis consumption is highly suggested to be responsible for brain anatomical and functional deviations from normal development. However, individuals with high genetic risk for developing psychotic disorders (such as schizophrenia) might be at particular risk for cannabis-related brain damage. Methods : Two articles from the IMAGEN consortium will be discussed, both liaising cannabis consumption and brain features. Results : First, French et al. (JAMA Psychiatry 2015 ;72(10) :1002-11) showed an interaction between early cannabis use and cortical thickness (CT) in males in 3 independent samples. Specifically, significant cannabis use by polygenic risk score (PRS) score interaction is found to be associated with CT (t=-2.6 ; p=0.009) in 459 males with greater PRS score being associated with decreased whole brain CT in cannabis users (R2 = 0.06 ; p=0.002) but not in no-users (p=0.9). Similarly, reduced CT was observed between very high users (ie > 61 lifetime occasions) and never users, only in individuals with high PRS scores (p=0.02 ; Cohen d=0.8), in an independent sample of 295 males adolescents. Finally, PRS x cannabis intake interaction is associated with increased cortical thinning between 14 and 19 years-old (i.e. change in CT) in a sample of 145 males (t=-2.36) from IMAGEN. No interaction effect was found on CT change in females (n=188 ; t=1.36 ; p=0.18). These results across 3 independent samples suggest gender differences with regard to the interaction of PRS x early cannabis consumption on CT and its changes during brain development. The second work stress the impact of early cannabis use on brain development between 14 and 19 years-old and psychotic symptoms in 706 adolescents from Imagen (n=1412 scans). Using a whole brain, yet focused onto regions involved in first episode psychosis, diffeomorphic morphometry approach, Yu et al. (in prep) identified greater shrinkage in the parahippocampus positively associated with psychotic symptoms assessed at 19 years-old (t= 4.2 ; p=0.018, Family Wise Error corrected at the peak level). Authors also found significant positive association between psychotic symptoms and cannabis intake (r=0.1, p=0.006). Finally, brain development in the parahippocampus significantly mediated the association of cannabis intake and psychotic symptoms (p=0.01). Conclusion : Brought together, these results suggest early cannabis consumption alters brain development, especially in genetically at-risk individuals which might be in turn responsible to subsequent psychotic symptoms and onset of schizophrenia.

S16

TARGETING THE ENDOCANNABINOID SYSTEM FOR THERAPEUTIC PURPOSES IN NEUROPSYCHIATRIC CONDITIONS

Leweke FM, Brain and Mind Centre, University of Sydney, 94 Mallett Street, Camperdown, Sydney, Australia, NSW 2050 markus.leweke@sydney.edu.au

Rohleder C(1), Lange B(1), Mueller JK(1), Koethe D(1)

(1) Central Inst of Mental Health, Medical Faculty Mannheim, Heidelberg Univ, Mannheim, Germany

Introduction: The discovery of the endocannabinoid system as a target of action for plant derived cannabinoids has triggered research into the role of this system in psychiatric disorders and led to a deeper insight into its role in psychosis and other neuropsychiatric conditions. The use of cannabis has been secured as a risk factor for the development of psychosis and schizophrenia. Based on this significant finding, a model of the role of the endocannabinoid system in the pathophysiology of schizophrenia has been suggested that paved the way to potential new treatment options involving this system. Methods: The evidence for a role of the endocannabinoid system in schizophrenia and other neuropsychiatric conditions is reviewed and the resulting potential treatment strategies are summarized. Results: While targeting of the endocannabinoid system using delta-9-tetrahydrocannabinol leads to psychotic symptoms both in healthy volunteers and in stabilized patients suffering schizophrenia, the endocannabinoid system itself is affected already at very early stages of psychosis but also in post-traumatic stress disorders and borderline personality disorders. It also plays an important role in energy metabolism and major components are involved in stress related responses and regulation of immune function. Based on these findings, so far, several controlled studies using cannabidiol, a phytocannabinoid compound that does not induce psychotomimetic states or addictive behaviour, have been performed in schizophrenia. These studies – as far as results are available already – have found a significant antipsychotic effect of cannabidiol in acute schizophrenia and indicated a new mechanism of action for the treatment of this condition. Conclusions: The endocannabinoid system plays an important role in several neuropsychiatric conditions and may serve as a target for the treatment of psychosis but also beyond that if large scale studies confirm initial evidence from early phase clinical trials. Funding: These studies have been funded by the Stanley Medical Research Institute, the European Commission and the German Ministry of Education and Research (BMBF).

S17

CORTICO-STRIATAL INTERACTIONS IN IMPULSIVE-COMPULSIVE DISORDERS

Robbins TW, Psychology and BCNI, University of Cambridge, Deot of Psychology, Downing St. Cambridge, CB23EB twr2@cam.ac.uk

Introduction Recent work in animals and humans has begun to delineate specific cortical-striatal pathways relevant to the decomposition of behavioural constructs of impulsivity and compulsivity underlying several mental health disorders. Discrete yet overlapping frontal-striatal circuits mediate broadly dissociable cognitive and behavioural components of these constructs. We illustrate this principle with two recent studies on impulsivity and compulsivity stimulated by studies in experimental animals using similar tasks and measures. Methods (i) We dissociated intrinsic neural correlates of fundamental mechanisms of behavioural control, 'waiting', (using a 4-choice serial reaction time task to assess premature responding) in comparison with 'stopping' via the stop-signal task. Neural correlates were mapped in 55 healthy volunteers and 32 young binge drinkers using a novel multi-echo resting-state functional MRI sequence and analysis that boosts signal-to-noise ratio. (ii) Patients with obsessive-compulsive disorder (OCD) were investigated using similar multiecho resting-state acquisition to obtain in vivo measures of functional connectivity in 44 OCD patients and 43 healthy comparison subjects. Graph theoretical models of brain networks were also derived. We measured cognitive flexibility (attentional set-shifting) and goal-directed performance (planning) using CANTAB tests. Results (i) Connectivity of limbic and motor cortical and striatal nodes mapped onto a mesial-lateral axis of the subthalamic nucleus (STN). Waiting impulsivity was associated with lower connectivity of STN with ventral striatum and subgenual cingulate, regions similarly implicated in rodent lesion studies. This network dissociated from fast reactive stopping involving hyper-direct connections of the pre-supplementary area and sub-thalamic nucleus also

implicated in alcohol misuse. (ii) Functional connectivity strength of striatal seed regions was related to cognitive flexibility and goal-directed performance. Reduced functional connectivity between the caudate and the ventrolateral prefrontal cortex was selectively associated with reduced cognitive flexibility. In contrast, goal-directed performance was selectively related to reduced functional connectivity between putamen and dorsolateral prefrontal cortex in OCD patients, as well as to symptom severity. Whole-brain data-driven, graph theoretical analysis revealed that nodes within the basal ganglia and cerebellum being more strongly inter-connected in OCD than in healthy controls. Conclusions These findings (i) show the relevance of fronto-striatal circuitry, extending to the STN, to impulsivity in alcohol misuse disorders and (ii) support major neuropsychological models of OCD by providing a direct link between intrinsically abnormal functional connectivity within functionally dissociable frontostriatal circuits and cognitive processes underlying OCD symptoms. (ii) They also show how basic findings on cortico-striatal function in experimental animals are translatable to human clinical studies. Supported by the Wellcome Trust.

S18

BRAIN CONNECTIVITY IN BIPOLAR DISORDER: TOWARD A NEW NEURAL MODEL AND IMPLICATIONS FOR TREATMENT

Phillips ML, Department of Psychiatry, University of Pittsburgh, Loeffler Building Room 305, 121 Meyran Avenue Pittsburgh PA 15213, 15213 phillipsml@upmc.edu

Introduction. Neuroimaging studies emphasize a pattern of elevated amygdala activity and reduced prefrontal cortical activity and prefrontal cortical-amygdala connectivity to emotional stimuli as a neural mechanism underlying emotional dysregulation in bipolar disorder (BD). Method. I will present multimodal neuroimaging data in adults with BD, and in adults and youth at risk for the disorder, that have facilitated further development of this neural model. Results. Specifically, in addition to the well-characterized pattern of abnormally elevated amygdala activity, and reduced prefrontal cortical-amygdala functional connectivity to emotional stimuli, our findings in the above populations indicate elevated activity in ventral striatum (VS) and left ventrolateral prefrontal cortex (vlPFC), and more widespread functional connectivity in largescale prefrontal cortical networks, during uncertain reward expectancy. The vlPFC is important for cue-outcome decision-making. Abnormally elevated activity in this region during uncertain reward expectancy may thus reflect a greater tendency to jump to conclusions about the possibility of obtaining future reward, and may underlie the greater tendency for fun-seeking and risk-taking in individuals with BD. In parallel, informed by a recent segmentation of the anterior limb of the internal capsule (ALIC) in non human primates, a key white matter tract connecting the prefrontal cortex, thalamus and brain stem, we show reduced fractional anisotropy (FA) in a specific component of the ALIC that carries descending fibers from left vlPFC to the habenula and brain stem in adults with BD. This latter finding may reflect abnormally reduced inhibitory regulation of brain stem (ventral tegmental area, VTA) dopaminergic input by prefrontal cortical afferents in individuals with BD, which, in turn, may contribute to the pattern of abnormally elevated, and most likely dopaminergically-modulated, activity in VS-prefrontal cortical reward circuitry that we observe in individuals with the disorder. Conclusion. Together, our data provide support for a neural model of BD that includes two main components: 1. abnormally elevated activity in VTA-VS-vlPFC circuitry during reward expectancy and positive emotional contexts, which is probably dopaminergically-modulated, and 2. abnormally reduced, regulatory vlPFC-amygdala, and vlPFC-VTA, connectivity in salient emotional contexts. These data have informed an ongoing study, in which we are targeting the left vlPFC with cathodal (inhibitory) transcranial direct current stimulation (tDCS) during performance of a reward task during fMRI as an intervention to help reduce risk-taking behavior in individuals with BD. Together, our findings provide new insights into neural mechanisms of BD, and neural targets for novel interventions for individuals with, and those at risk for, the disorder. This research was funded by grants to MLP: R01MH073953, R01MH059929, R01MH10004, P50MH106435, R21MH108421, R01MH060952.

S19

THE EFFECTS OF CANNABIS ON BRAIN CONNECTIVITY AND IMPLICATIONS FOR TREATING CANNABIS DEPENDENCE

Bloomfield MA, Division of Psychiatry, University College London, Maple House Tottenham Court Road London, W1T 7NF m.bloomfield@ucl.ac.uk

Heavy cannabis use, especially during adolescence in associated with a range of adverse psychiatric outcomes including psychosis, affective disorders and dependence. Exposure to the active ingredients of cannabis, the phytocannabinoids, has effects on a range of pharmacological systems including the endocannabinoid and dopamine systems. Thus it thought that disruption of these systems provides a mechanism underlying the vulnerability to mental illness associated with cannabis. In parallel, there is much interest in therapeutically exploiting the endocannabinoid system across a broad range of disorders. There is increasing evidence that cannabinoid exposure is associated with altered brain connectivity and it is therefore important to understand these effects in terms of the potential harmful and proposed therapeutic effects of cannabinoids. The current state of knowledge in the field will be presented. This will be followed by the presentation of new multimodal magnetic resonance imaging (MRI) research data indicative of differences in higher order network stability associated with cannabis use and how this relates to the cognitive and pharmacological effects of cannabis. The clinical implications of these findings will be considered with a focus on treating cannabis use disorders.

S20

CONNECTOMICS OF SCHIZOPHRENIA

Bullmore ET, Dept Psychiatry, University of Cambridge, Herchel Smith Building for Brain & Mind Sciences Cambridge Biomedical Campus, CB2 0SQ etb23@cam.ac.uk

Introduction The idea of schizophrenia as a brain network disorder goes back to the dawn of psychiatry, long before we were technically able to measure or analyse connectomes as precisely as we now can. Methods Graph theoretical methods for measuring the complex topology of brain networks - across a range of scales and species - are used to demonstrate a trade-off between biological cost and topological integration. Results High cost and high value hubs of the connectome are often impacted by brain disorders, including schizophrenia. Adolescent maturational changes in cortical myelination are concentrated on the hubs of the connectome and are associated with expression of genes enriched for risk of schizophrenia. Conclusions Genetically programmed adolescent development of human brain network hubs may be relevant to the pathogenesis of schizophrenia.

S21

THE CHALLENGES OF PSYCHOPHARMACOLOGY IN DEMENTIA

Burns A, School of Biological Sciences, Faculty of Biology, Medicine and Health, 3.304 Jean McFarlane Building The University of Manchester Oxford Road Manchester, M13 9PL alistair.burns@manchester.ac.uk

Special consideration needs to be given to the psychopharmacology of dementia and related disorders. There are aspects which are unique to dementia such as treatment of Alzheimer's disease, vascular dementia and Lewy body disease. In addition, there is much that can be learned from an approach to the treatment of comorbid conditions in those illnesses such as depression, anxiety and agitation. This presentation will look at the evidence behind these treatments and discuss implications for the future. In addition, bespoke evidence for treating so-called functional disorders such as depression and schizophrenic like illnesses in older people will look at the particular needs of the older population and the task of developing bespoke treatment approaches. The current landscape of dementia practice and care will be summarised.

S22

EXPLORING THE RELATIONSHIP BETWEEN NEUROPATHOLOGY AND SYMPTOMS

Passamonti L, Dept of Clinical Neurosciences, Univ of Cambridge, Herchel Smith Building Robinson Way Cambridge Biomedical Campus Cambridge, CB2 0SZ lp337@medschl.cam.ac.uk

I will present our recently funded Medical Research Council (MRC) project which aims at treating impulsivity in progressive supranuclear palsy (PSP), a devastating parkinsonian syndrome associated with abnormal accumulation of the tau protein in the brain. Despite the fact that PSP patients can be severely bradykinetic and rigid, the same patients can also display impulsive and reckless behaviour that puts them at risk of falls, injury, and choking, especially in the context of balance and swallowing difficulty. The underlying causes of impulsivity in PSP are multi-factorial. However, there is converging evidence that alterations in the noradrenergic system may play a fundamental role. Animal models and our research in Parkinson's disease (PD) have indeed shown that changes in the noradrenaline (NA) transmission are associated with impulsivity and that this can be reduced by medications enhancing NA transmission (i.e., atomoxetine). The aims of the project are to: 1. Test the hypothesis that impulsivity in PSP results from changes in the noradrenergic system. 2. Test the hypothesis that enhancing NA levels via atomoxetine reduces impulsivity in PSP. Our project will test these hypotheses by providing convergent data from: (1) post-mortem studies from our longitudinal phenotyping studies and brain banking; (2) advanced neuroimaging techniques, and (3) computational analytical methods applied to psycho-pharmacological research. We will integrate advances at the microscopic (pathology), mesoscopic (brain structure), and macroscopic (brain function & behaviour) level in three conceptually linked but concurrently executed phases of the project. During the talk, I will describe in more detail the post-mortem studies which aim to correlate molecular, synaptic, and cellular markers of neurodegeneration and noradrenergic function with ante-mortem measures of impulsivity in our PSP archival cases from the Cambridge's Brain Bank. Using molecular, cellular, neuroimaging, and psycho-pharmacological techniques, we aim to build a "bridge" between the neuro-pathological and symptomatic level in PSP. The ultimate goal of our project is to advance from purely descriptive accounts of a common behavioural symptom in PSP to predictive and mechanistic models with the potential for a novel, rational, and individualised therapy.

S23

REVERSE-TRANSLATION OF QUANTITATIVE BIOLOGY IN NEURODEGENERATIVE DISEASE

Li J, Translational & Integrative Neuroscience, Eli Lilly and Company Limited, Erl Wood Manor, Sunninghill Road, Windlesham, GU20 6PH li_jennifer@lilly.com

There is a clear unmet medical need for treatments of neurodegenerative diseases such as Alzheimer's and Parkinson's Disease, which now represent one of the leading causes of morbidity and mortality in the developed world. These diseases may originate from the misprocessing and/or accumulation of proteins such as amyloid, tau and synuclein. Much attention has been focused on disease modifying treatments that directly attempt to prevent the progressive molecular changes that typify these conditions. Understanding of neurodegenerative disorders is reaching an inflection point where it is becoming clearer how presentation of symptoms in individual patients relates to molecular pathology, cell damage and dysfunction in specific brain regions and networks. An increasingly powerful set of biomarkers now allow these parameters to be measured in living individuals. Human neurodegenerative disease research is nearing an era where the impact of disease on neuronal and functional viability is becoming truly quantitative. This talk will focus on how such clinical findings can be used to inform preclinical disease research. In patients, quantitative biological measures of pathological burden and symptomatic deficits are being studied at all levels of function from digital biomarkers, MRI and PET neuroimaging, electrophysiological measures, and biofluid assessments. Taken together, these measures suggest that the pathological burden of neurodegenerative disease may begin many years before the onset of patient or caregiver-identified symptoms. There may be a prolonged phase of neuronal dysfunction that precedes overt neurodegeneration and suggests that there may also be opportunities for disease intervention therapies related to the fostering of "synaptic health", via manipulation of innate immunity, inflammatory or neuroplastic mechanisms that do not directly target the hypothetical toxic protein

species. Aging is also implicated as a significant risk factor for neurodegeneration. With a growing aging population, understanding changes in functional aspects such as cognitive reserve, network plasticity measures, and functional connectivity changes will become ever more important in the search for new symptomatic therapies. All of these findings are informing a new generation of animal modeling, where rodent transgenic models are being developed with more appropriate presentation of neuropathology, and equivalent preclinical measures to those described above are being validated. This presentation will highlight a number of translational approaches being developed such as cognitive behavioural models, electrophysiology approaches, measures of neurotransmitter efflux, and brain functional connectivity measures in freely-moving rodents. Measuring functional consequences of this neuropathology, alongside techniques such as tau PET imaging, will aid understanding of symptomology and therapeutic approaches.

S24

DEVELOPING A QUANTITATIVE APPROACH TO SYMPTOMOLOGY OF SOCIAL WITHDRAWAL

Kas MJ, Groningen Inst for Evolutionary Life Sciences, Univ of Groningen, PO Box 72 9700 AB Groningen, The Netherlands m.j.h.kas@rug.nl

Introduction: Most mental health conditions are still classified and diagnosed solely based on the symptoms observed, as there are few objective biomarkers for these conditions as there are for other conditions, such as diabetes. Furthermore, many different neuropsychiatric diseases share symptoms, which makes it difficult to understand what is the underlying biological cause of a specific disease. For example, social withdrawal is an early symptom of a wide variety of neuropsychiatric disorders, including Schizophrenia and Alzheimer's Disease. At this stage, we do not have an idea, whether the biological cause for social withdrawal in Alzheimer's disease differs from that in schizophrenia. As part of PRISM, a recently funded Innovative Medicine Initiative EU project, we are implementing quantitative measures for social withdrawal to cluster patients on the basis of biological parameters. Furthermore, by means of a pre-clinical approach, findings from the human studies can eventually be back-translated to rodent species for further neurobiological studies. Methods: For human subjects, smartphone technology has been developed to provide longitudinal objective measures of social exploration and communication to establish novel measures of social withdrawal. In PRISM, both Alzheimer's Disease and Schizophrenia patients will be assessed using this technology. Back-translation of human social withdrawal findings will be directed at changes in social group dynamics longitudinally studied in rodent colonies. Results: Preliminary findings indicate that differences in social readouts based on smartphone technology in humans and on social group dynamics in rodents can be obtained. Conclusions: The overall objective of the PRISM project is to develop a quantitative biological approach to the understanding and classification of neuropsychiatric diseases to accelerate the discovery and development of better treatments for patients. The concept of our proposal is to define a set of quantifiable biological parameters for social withdrawal and cognitive deficits to cluster and differentiate schizophrenia and Alzheimer's disease. Here, we put forward technological innovations to assess objectively social withdrawal in human subjects and rodent species. The PRISM project (www.prism-project.eu) has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115916. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA. This publication reflects only the authors' views neither IMI JU nor EFPIA nor the European Commission are liable for any use that may be made of the information contained therein.

S25

TARGETED TREATMENTS FOR COGNITIVE DYSFUNCTION IN BIPOLAR DISORDER

Young A, Centre for Affective Disorders, Dept of Psychological Medicine, IoPPN, King's College London, PO72, De Crespigny Park, Denmark Hill, London, SE5 8AF Allan.young@kcl.ac.uk

Objectives: To understand the neurocognitive deficits of bipolar disorders; To understand the impact of emotional regulation on functional outcomes; To review the treatment options to improve functional outcomes Methods: A critical review of the neurocognitive and functional studies carried out in individuals with bipolar disorder. Results: It has been demonstrated that impairment in cognitive domains

can still be present during euthymic or sub-syndromal phases of bipolar disorder and could be a trait-related neuropsychological deficit. Most studies investigating the association between neurocognition and functional outcomes have found that cognitive deficits significantly predicted functional outcomes but to a lesser extent than clinical symptoms. Moreover, neurocognitive dysfunction is present early in the course of the disease and may increase with illness progression. One of the most consistent finding is a reduced response inhibition. Overall, the literature points to executive function deficits in type I Bipolar Disorder associated with functional abnormalities in the prefrontal cortex. Of interest, social cognition, as reflected by facial emotion recognition, is also impaired in some bipolar subjects, and this may play a significant role into the clinical-functional gap observed in these patients. Conclusions: These data points to the importance that should be given to the development of more specific clinical treatments aiming at improving the functional outcomes in bipolar disorder. Techniques such as social and cognitive remediation should be explored in this diagnostic group. Grant funding (past and present): NIMH (USA); CIHR (Canada); NARSAD (USA); Stanley Medical Research Institute (USA); MRC (UK); Wellcome Trust (UK); Royal College of Physicians (Edin); BMA (UK); UBC-VGH Foundation (Canada); WEDC (Canada); CCS Depression Research Fund (Canada); MSFHR (Canada); NIHR (UK).

S26

NEUROBIOLOGICAL UNDERPINNINGS OF COGNITIVE ENHANCEMENT TREATMENT IN MOOD DISORDERS

Miskowiak KW, Psychiatric Centre Copenhagen, Rigshospitalet, Dep. 6233, Capital Region of Psychiatry, Blegdamsvej 9, 2100 kamilla@miskowiak.dk

Cognitive dysfunction is an emerging treatment target in depression and bipolar disorder but there are no available cognition treatments with reliable, enduring effects. Impaired neuroplasticity is a putative neurobiological pathway underlying cognitive deficits and mood symptoms. Novel treatments with rapid and enduring effects on neuroplasticity such as erythropoietin (EPO) therefore hold great promise for targeting both cognition and mood symptoms in these patients. We conducted two prospective randomized, double-blind, placebo-controlled clinical trials of the effects of eight weekly infusions of EPO (40,000 IU) (N=40) or saline (N=39) on cognitive deficits and mood symptoms in patients with treatment-resistant depression or bipolar disorder in remission. Cognition and mood symptoms were assessed at baseline (week 1), after treatment completion (week 9) and at follow-up (week 14). Functional and structural magnetic resonance imaging (MRI) assessments were conducted at weeks 1 and 14 to assess the underlying neuronal mechanisms of treatment-related improvements in cognition. Erythropoietin improved verbal memory, speed of complex cognitive processing across attention, memory and executive function and the recognition of happy facial expressions in comparison with saline. These effects occurred in the absence of change in mood symptoms and prevailed at the six weeks follow-up assessment after treatment completion. Structural MRI revealed that the EPO-associated memory improvement was mediated by reversal of subfield volume loss in the left hippocampus. In addition, fMRI showed that improvements of spatial memory and working memory in EPO-treated patients were accompanied by increase in task-related dorsolateral prefrontal and temporo-parietal activity as well as suppression of default mode network activity. The findings highlight EPO as a promising candidate treatment for cognitive dysfunction in mood disorders. Putative neuronal underpinnings were structural increase in the left hippocampus and neural activity increase in dorsolateral prefrontal and temporo-parietal regions. Together, the findings provide novel evidence for potential circuitry-based biomarkers for therapeutic effects of cognition treatments in mood disorders. Sources of financial sponsorship of the studies: The study was funded by the The Danish Council for Independent Research, Nordisk Foundation, Beckett Fonden, and Savværksejer Juhl's Mindefond.

S27

ABNORMALITIES IN EMOTIONAL PROCESSING IN MOOD DISORDERS – NOVEL TREATMENTS

Harmer CJ, Psychiatry, University of Oxford, Warenford Hospital, Oxford, OX3 7JX catherine.harmer@psych.ox.ac.uk

Introduction: Negative affective bias is commonly reported in depression, where patients are more likely to focus on, interpret and remember negative vs positive emotional information. Early effects of conventional antidepressant drug treatments on negative affective bias have been reported in both behavioural and neuroimaging measures and these early effects are predictive of later changes in clinical ratings of depression. Such findings raise the intriguing possibility that early remediation of negative bias may be a mechanism of antidepressant drug action and could be harnessed to screen and assess effects of novel candidate treatments for depression. Methods: The current talk will focus on the potential application of these findings to the characterisation of novel or underexplored treatments for depression including a focus on the NMDA, nociception and dopamine systems. Results: The catecholamine reuptake inhibitor bupropion (licensed in the UK for smoking cessation and in the US also for depression) was assessed in patients with major depression over a 6 week treatment period. Patients with major depression showed negative biases in emotional processing and reduced sensitivity to reward in a probabilistic learning task prior to treatment. Bupropion reduced negative bias in depression including a reduction in the misclassification of faces as sad and increasing memory for positive items. These effects were seen after 2 weeks and maintained after 6 weeks of treatment. However, in the reward task, sensitivity to rewarding information was initially reduced after 2 weeks and then normalised (to the level in healthy volunteers) after 6 weeks of treatment. In a parallel study in healthy volunteers, one dose of bupropion also reduced the processing of negative affective information (such as the misclassification of facial expressions as sad) but decreased sensitivity to reward relative to placebo. These findings together suggest that drugs useful in the treatment of depression have early effects on emotional processing but the effects on reward are delayed. As such these processes may rely on separable underlying processes. Conclusions: Compared to clinical rating scores, objective measurement of emotional and cognitive function with behavioural assessment and neuroimaging may provide more information about the early effects of antidepressants. These early effects may help understand mechanisms and profiles of established and novel treatments for depression. Support: The bupropion study was supported by an investigator initiated grant from Johnson & Johnson.

S28

PSYCHOLOGICAL TREATMENT OF COGNITIVE ABNORMALITIES IN MOOD DISORDERS

Porter RJ, Psychological Medicine, University of Otago, Christchurch, PO Box 4345 Christchurch, 8140 richard.porter@otago.ac.nz

Douglas (1)

(1) Department of Psychological Medicine, University of Otago, Christchurch

Recurrent major depressive disorder (MDD) and bipolar disorder (BD) are associated, in a percentage of cases, with significant cognitive dysfunction, even during remission. This impairment is, to an extent, independent of mood symptoms, has significant implications for prognosis, and exerts an effect on overall functioning. This presentation will outline the theoretical and neurobiological rationale for psychological treatments which focus on the treatment of cognitive dysfunction. Data will be presented suggesting that there is little evidence of traditional psychotherapies having a beneficial effect on cognitive function in depression. Cognitive Behavioural Therapy (CBT), for example, has been shown to have minimal effect on cognitive function, regardless of effect on mood symptoms (Porter, R. J., et al. (2016) Psychol Med 46(2): 393-404.). In contrast, meta-cognitive therapy, which includes specific attentional training, improved aspects of working memory more so than CBT (Groves, S. J., et al. (2015). Depress Anxiety 32(6): 437-444.). Data will also be presented regarding the effects of 18 months of Interpersonal and Social Rhythms Therapy on cognitive function in bipolar disorder. Preliminary studies using cognitive remediation based techniques in mood disorders will be presented, with focus on clinical contexts in which cognitive remediation may be particularly likely to be important. The methodology of such studies is crucial and

this will be discussed including reference to rates of cognitive impairment in different samples of patients with mood disorders and the implications of this for sample selection in studies with primary cognitive outcomes. Funding - Health Research Council of New Zealand, Lotteries Health NZ, University of Otago, Canterbury District Health Board.

S29

BRAIN-GUT-MICROBIOTA AXIS: A NOVEL THERAPEUTIC TARGET

Dinan TG, Psychiatry, University College Cork, Cork University Hospital Wilton, Cork, Ireland, C1 ORE t.dinan@ucc.ie

Introduction: Evidence is accumulating to suggest that gut microbes may be involved in neural development and function, both peripherally in the enteric nervous system and centrally in the brain. While evidence is still limited in psychiatric illnesses, there are rapidly coalescing clusters of evidence which point to the possibility that variations in the composition of gut microbes may be associated with changes in the normal functioning of the nervous system. Methods: A combination of studies in rodents and healthy volunteers will be presented. Results: Germ-free animals show aberrant development of the brain monoaminergic system together with memory deficits and autistic patterns of behaviour. These deficits can be partially normalised if there is early gut colonisation. There are marked differences in the gut microbiota between patients with major depression and healthy controls. Following a cocktail of antibiotics we conducted a faecal microbiota transplant in rats with faeces from depressed patients or healthy controls. Those rats receiving a transplant from depressed patients developed a depressive phenotype with alteration in corticosterone release and tryptophan metabolism. Bacteria that may influence the capacity to deal with stress, reducing anxiety, perhaps positively impacting on mood and are now called psychobiotics. The mechanisms of psychobiotic action are gradually being unravelled. It has been show that Lacobacillus rhamnosus has potent anti-anxiety effects in animals and does so by producing major changes in the expression of GABA receptors in the brain. The changes in these receptors are mediated by the vagus nerve which connects the brain and gut. When this nerve is severed no effect on anxiety or on GABA receptors is seen following psychobiotic treatment. Conclusions: Communication between the brain and gut is bidirectional and complex. Increased understanding of this axis and the role of the gut microbiota may aid the development of therapies not just for functional bowel disorders but for mood disorders also. That bacteria might have a positive mental health benefit is now becoming clear. Whether psychobiotics are capable of acting like and in some circumstances replacing antidepressants remains to be seen. Acknowledgement: The author is supported in part by Science Foundation Ireland in the form of a centre grant (Alimentary Pharmabiotic Centre Grant Number SFI/12/RC/2273); by the Health Research Board of Ireland (Grant Numbers HRA_POR/2011/23 and HRA_POR/2012/32) and received funding from the European Community's Seventh Framework Programme Grant MyNewGut under Grant Agreement No. FP7/2007-2013.

S30

EFFECTS OF ANTIPSYCHOTIC TREATMENT ON IMMUNE ACTIVATION IN THE ADIPOSE TISSUE

Mondelli V, Psychological Medicine, IoPPN, King's College London, Maurice Wohl Clinical Neuroscience Institute, Cutcombe road London, SE5 9RT valeria.mondelli@kcl.ac.uk

Calevro A(1), Cotel M(1), Vernon A(1)

(1) As presenting author

Introduction Antipsychotic medications have been recently suggested to influence immune activation both in the periphery and central nervous system (CNS). However, the effect of chronic antipsychotic treatment on peripheral tissue such adipose tissue remains still unclear. Adipose tissue is known to play an important role in the development of systemic inflammation and mitochondrial dysfunction. Macrophages in the adipose tissue display several phenotypic markers including F4/80+. Translocator Protein, TSPO, is a mitochondrial membrane protein which has been recently considered a marker of neuroinflammation as its density is elevated in activated microglia, but its expression has not been yet studied in adipose tissue. In this study we looked at the expression of F4/80+, TSPO, and inflammatory cytokines in rat adipose tissue

following chronic antipsychotic treatment. Our aim was to look at the presence of inflammation in the periphery as the same rats previously had shown microglial activation in the brain. Methods We collected visceral adipose tissue from a group of 24 male Sprague-Dawley rats treated in a previous study (Mondelli et al., 2013, Cotel et al., 2015) with vehicle (n=8), haloperidol (2 mg kg per day, n=8), or olanzapine (10 mg kg per day, n=8), using osmotic minipumps, for 8 weeks. We assessed levels of the following pro- and anti-inflammatory cytokines in the adipose tissue: tumor necrosis factor-α (TNFα), interleukin (IL)-1β, IL-6, IL-5, IL-4, IL-10 and KC/GRO, a chemokine (CXC) also known as CXCL1. Cytokine levels were measured using a electrochemiluminescence immunoassay MSD Mesoscale. We performed Western Blot analysis using TSPO antibody and F4/80+ antibody; beta-actin was used for housekeeping expression. The density of the bands was calculated using ImageJ program. Results Amongst the cytokines, only IL-6 was significantly up-regulated in olanzapine animals compared to vehicle animals (One-Way ANOVA with Bonferroni post hoc test $p<0.05$). Interestingly, the olanzapine group showed also higher F4/80+ when compared with the haloperidol group ($p<0.05$). We did not find any significant difference in TSPO expression either between haloperidol and vehicle or between olanzapine and vehicle ($p>0.05$). Conclusions Our preliminary results suggest a possible increased inflammation and macrophagic activation in the adipose tissue following olanzapine (based on the IL-6 and F4/80+ data) but not haloperidol treatment. These findings suggest that olanzapine tends to increase/activate inflammation in the adipose tissue with possible important consequences in terms of metabolic dysregulation.

S31

EFFECTS OF PREBIOTICS ON THE BRAIN

Burnet P, Dept of Psychiatry, Univ of Oxford, Oxford, OX3 7JX phil.burnet@psych.ox.ac.uk

We are exploring the central effects of prebiotics, dietary fibres that proliferate the indigenous beneficial enteric microbiota. Since these microbes influence host immunity, we first explored whether galacto-oligosaccharides (Bimuno, B-GOS) influence endotoxin-mediated sickness behaviour, anxiety and inflammatory responses in mice. Animals injected with lipopolysaccharide (LPS) displayed reduced locomotor activity compared to saline injected controls, but this was not observed in mice that had received dietary B-GOS for 3 weeks prior to LPS injection. Twenty-four hours after the LPS injection, mice that had received a non-supplemented diet displayed anxious behaviour in the Light/Dark box paradigm, compared to BGOS-fed animals. The ingestion of B-GOS, also suppressed the LPS-meditated elevation of pro-inflammatory cytokines (TNFa, IL-1b, IL-6). We therefore propose that B-GOS intake has anxiolytic actions that involve suppression of the pro-inflammatory response. The effects of B-GOS and another prebiotic, fructo-oligosaccharides (FOS), on the secretion of the stress hormone, cortisol, and emotional processing in healthy volunteers was also investigated. Forty-five healthy volunteers received one of two of the prebiotics or a placebo daily for 3 weeks. The salivary cortisol awakening response was sampled before and after prebiotic / placebo administration. On the final day of supplementation participants completed a computerised task battery assessing the processing of emotionally salient information. The salivary cortisol awakening response was significantly lower after B-GOS intake compared with placebo. Participants also showed decreased attentional vigilance to negative versus positive information in a dot-probe task after B-GOS compared to placebo ingestion. No effects were found after the administration of FOS, which may reflect the greater potency of B-GOS in proliferating the gut Bifidobacteria. Finally, the influence of B-GOS and FOS on brain glutamate NMDA receptor levels and cognitive flexibility were examined. Rats fed with either FOS or B-GOS expressed greater levels of hippocampal NMDA receptor GluN1 and GluN2A subunits than controls. Both prebiotics increased hippocampal BDNF expression, which corroborates the neurotrophic actions of gut bacteria shown with probiotics. Animals fed with B-GOS also show elevated cortical NR1 subunits and D-serine, compared to FOS and control rats. In the attentional set-shifting task B-GOS-fed rats improved shifting from an intra-dimensional to an extra-dimensional set, relative to controls. This suggests that the BGOS-mediated elevation of NR1 and D-serine in the frontal cortex, lead to functional NMDA receptors and improved attention. Further studies are therefore needed to test the utility of B-GOS supplementation in the treatment of stress-related disorders and cognitive decline.

S32

INTESTINAL INFLAMMATION, THE MICROBIOME, AND HUMAN NEUROPSYCHIATRIC DISORDERS-RESULTS OF A RANDOMIZED TRIAL OF A PROBIOTIC PREPARTATION FOR THE PREVENTION OF MANIA

Yolken RH, Neurovirology, Johns Hopkins School of Medicine, 600 N Wolfe St, Baltimore Md, 21287 rhyolken@gmail.com

Dickerson FB(1)

(1) Sheppard Pratt Health System. Baltimore MD

Introduction:. Acute mania is a serious psychiatric disorder with a high level of morbidity and mortality. Previous studies indicate that many episodes of acute mania are associated with evidence of inflammation, particularly at the level of the gastrointestinal tract. Individuals undergoing an episode of mania are at a very high risk of a second episode within a 6 month period of time. The ability to prevent these recurrent episodes would represent a major improvement in the care of individuals with mania. Methods :We hypothesized that preventing intestinal inflammation would result in a diminution of episodes of mania recurrence and that probiotic treatment would be a safe and effective means of accomplishing this prevention. We thus enrolled 66 individuals hoapitalized with acute mania in a placebo-controlled double blind study in which individuals received a daily administered probiotic preparation containing more than 108 colony forming units of Lactobacillus GG and Bifidobacterium lactis strain or an identical-appearing placebo. Follow-up was performed weekly over a 6 month period. The primary outcome measure was a reduction in the incidence of re-hospitalization. Secondary outcome measures were changes in social functioning and clinical severity scores. Results: We found that the administration of the probiotic preparation resulted in a significant decreased in the rate of re-hospitalization over the 6 month study period as compared to placebo(Hazard ratio=0.39; 95% CI 0.17, 0.90, p=.028 adjusted for age, gender, race, and socio-economic status). Probiotic administration was also associated with a decrease in the number of re-hospitalizations and an improvement in social functioning. Probiotic administration was not associated with a change in symptom scores assessed at the end of the study period. Conclusions: Probiotics and other modalities which can modulate intestinal inflammation have a great deal of potential for the prevention of episodes of mania. Their role in the management of individuals with bipolar disorder and other psychiatric disorders warrant further investigation. Given their low cost and low rate of side effects, probiotic preparations have the potential to play a major role in the management of serious psychiatric disorders and decrease the morbidity associated with these disorders. This work was supported by the Stanley Medical Research Institute.

S33

MARKERS OF POTENTIAL THERAPEUTIC EFFICACY FOR NEGATIVE AND COGNITIVE SYMPTOMS

Neill JC, Division of Pharmacy & Optometry, University of Mnachester, Oxford Road, Manchester, M13 9PT joanna.neill@manchester.ac.uk

Grayson B(1), Harte MK(1), Cadinu D(1), Podda G(1)

(1) As presenting author

Although antipsychotic drugs alleviate psychotic symptoms of schizophrenia, cognitive deficit and negative symptoms remain an unmet clinical need (Keefe et al. Arch Gen Psychiatry 2007; 64:633-647). In spite of significant efforts by academic groups and the Pharmaceutical Industry, no drug has yet received a license for these indications (see Talpos, Drug Discov Today, 2017; doi: 10.1016/j.drudis.2017.04.014 for recent review). Several key issues remain unresolved, for example, the failure of positive results with new drug candidates in preclinical to Phase II trials to translate into success in large Phase III trials (Bespalov et al. Nat Rev Drug Discov 2016; 15(7):516) and finding a biomarker enabling identification of patients that will transition from an ultra high risk (UHR) state to psychosis. Recent work by Carol Tamminga and colleagues has identified subgroups of patients according to brain based biomarkers not in accordance with their clinical diagnoses (Clementz et al. Am J Psychiatry 2016; 173:373-384). The authors suggest that these subtypes of patients are likely to benefit from differential treatment strategies. The key to development of improved therapies is improved animal models that mimic the human condition in terms

of behaviour and pathology and that predict efficacy of novel treatments in patients. The benefit of using animals is development of different models that can represent these separate clinical biotypes. Long-standing research in our laboratory shows that sub-chronic treatment (2 mg/kg ip for 7 days followed by 7 days wash-out) with the un-competitive NMDAR antagonist PCP (Phencyclidine) mimics cognitive and negative symptoms in female Lister Hooded rats, along with associated pathological changes (Neill et al. Pharmacol & Ther 2010;128(3): 419-432; Neill et al. Eur Neuropsych 2014; 24:822-835). These effects are attenuated by atypical antipsychotics, specifically low dose risperidone and novel targets but not by classical antipsychotics. An emerging project in our laboratory shows that maternal immune activation (mIA) induces pathological and behavioural deficits in the offspring that are sex and time dependent and may represent the developmental trajectory of the illness (see Grayson et al. and Oladipo et al, this meeting). Our latest results with novel targets in the scPCP model will be evaluated in this presentation, and our recent work with the mIA model. This presentation will consider the evidence that these two animal models may represent separate biotypes, will enhance our understanding of the psycho and neuropathology of specific negative symptom and cognitive domains and allow early detection of novel pharmacological targets. The authors are grateful to Autifony Therapeutics Ltd and Roche for support.

S34

METABOLOMICS APPROACH TO STUDY THE DEVELOPMENT OF METABOLIC CO-MORBIDITIES IN FIRST-EPISODE PSYCHOSIS

Oresic M, Turku Centre for Biotechnology, University of Turku, Tykistokatu 6, FI-20520 matej.oresic@utu.fi

Hyötyläinen T(1), Mantere O(2), Pöhö P(3), Kieseppä T(4), Suvisaari J(4), Suvitaival T(5), Mattila I(5)

(1) Department of Chemistry, Örebro University, 702 81 Örebro, Sweden; (2) Department of Psychiatry, McGill University, Montréal, QC, H3A 1A1, Canada ; (3) Faculty of Pharmacy, University of Helsinki, Helsinki, FI-00014, Finland; (4) Mental Health Unit, National Institute for Health and Welfare, Helsinki, FI-00271, Finland; (5) Steno Diabetes Center Copenhagen, Gentofte, DK-2820, Denmark

Psychotic patients are at high risk for developing obesity, metabolic syndrome and type 2 diabetes. These metabolic co-morbidities are hypothesized to be related to both treatment side-effects as well as to metabolic changes occurring during the psychosis. Earlier metabolomics studies have shown that blood metabolite levels are predictive of insulin resistance and type 2 diabetes in the general population as well as sensitive to the effects of antipsychotics. Here we aimed to identify the metabolite profiles predicting future weight gain and other metabolic abnormalities in psychotic patients. We applied comprehensive metabolomics to investigate serum metabolite profiles in a prospective study setting in 36 first-episode psychosis patients during the first year of the antipsychotic treatment and 19 controls. While corroborating several earlier findings when comparing cases and controls and the effects of the antipsychotic medication, we also found that prospective weight gain in psychotic patients was associated with increased levels of triacylglycerols with low carbon number and double bond count at baseline, i.e. lipids known to be associated with increased liver fat. Our study suggests that metabolite profiles may be used to identify the psychotic patients most vulnerable to develop metabolic co-morbidities, and may point to a pharmacological approach to counteract the antipsychotic-induced weight gain. This project has received funding from the European Union's Seventh Framework Programme for project METSY - Neuroimaging platform for characterisation of metabolic co-morbidities in psychotic disorders (no. 602478).

S35

EXPLORING THE GENETICS OF TREATMENT RESISTANCE IN SCHIZOPHRENIA

Walters JTR, MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Hadyn Ellis Building Maindy Road Cardiff, CF24 4HQ waltersjt@cf.ac.uk

Background In the last 5 years important advances have been made in elucidating the genetic contributions to neuropsychiatric disorders. The advent of personalised medicine raises the question of whether genetics may be helpful in defining sub-groups of patients with differential responses to treatments. In this study we use large-scale genetic data to address this issue in the context of treatment-resistant schizophrenia (TRS). Methods CLOZUK is a TRS sample (n= 15000) recruited from routinely

collected blood samples of those taking clozapine in the UK. These samples underwent genotyping on the Illumina OmniExpress array with standardised QC. We perfomed a genome-wide association study (GWAS) of the CLOZUK sample compared to 25000 UK-based control samples. This sample was then compared with a generic schizophrenia sample GWAS in order to identify genetic associations that are specific to TRS. We further characterised the TRS genetic signature by exploring its correlation with the polygenic signal of other neuropsychiatric and behavioural phenotypes using LD score regression (LDSR). Results The CLOZUK GWAS generated 20 genome-wide significant loci, four of which are novel. There was strong genetic correlation between the CLOZUK and independent PGC schizophrenia datasets (0.95). In comparing TRS GWAS results with those of generic schizophrenia we detected SNP-based heritability and one genome-wide significant signal. Using LDSR we demonstrate genetic enrichment in TRS for alleles associated with lower educational attainment and behavioural phenotypes. Discussion These analyses demonstrate for the first time that there is SNP-based heritability of TRS when compared to generic schizophrenia. Furthermore we show genetic enrichment for alleles associated with lower educational attainment within the TRS sub-group. These findings suggest overlap between the aetiology of TRS and lower educational attainment and raise the possibility of genetically-informed stratified medicine in respect of treatment response in schizophrenia. This work is funded by an MRC stratified medicine grant: STRATA (MR/L011794/1) and EU FP7 funding (CRESTAR: grant agreement n° 279227). The work at Cardiff University was also funded by Medical Research Council (MRC) Centre (MR/L010305/1), and Program Grant (G0800509).

S36

THE TRANSDIAGNOSTIC NEUROBIOLOGY OF PSYCHOSIS AND TREATMENT RESPONSE: PET AND MRI IMAGING FINDINGS IN SCHIZOPHRENIA AND BIPOLAR AFFECTIVE DISORDER

Howes OD, Psychiatric Imaging Group, IoPPN KCL/ MRC LMS ICL, Box 67, IoPPN, KCL, Camberwell, London SE5 8AF and MRC LMS, ICL, Hammersmith Hospital, London W12 0NN, SE5 8AF oliver.howes@kcl.ac.uk

Introduction Psychosis is seen in a number of disorders and treated with the same drugs. Understanding the neurobiology underlying psychosis across diagnoses and in treatment response and non-response is important to help guide the development of new treatments and biomarkers for treatment response. Method Two cohorts of patients, one with a diagnosis of schizophrenia and another with a diagnosis of bipolar affective disorder and a history of psychosis received 18F-DOPA PET and [1H]-MR spectroscopy imaging. A sub-sample of these then commenced antipsychotic treatment and received clinical follow-up to determine response. In a separate cross-sectional study, patients with schizophrenia with established treatment resistance and treatment response also received the same imaging measures. The potential of targeting the autoreceptor regulatory control of dopamine synthesis using low dose apomorphine was tested in a cohort of healthy volunteers. Results Striatal dopamine synthesis capacity (Kicer) was significantly elevated in both bipolar ($p<0.05$) and schizophrenia ($p<0.05$) groups, compared to control.. There was no significant difference in dopamine synthesis capacity between bipolar and schizophrenia groups. Kicer was significantly positively correlated with positive psychotic symptom severity ($r=0.5$, $p<0.01$). In the cohort that went on to treatment there was a significant effect of group on Kicer in associative striatum ($F(2,37)=6.04$, Kicer was significantly higher in responders than both non-responders (cohen's d effect size=1.3) and healthy volunteers (cohen's d=1.1). There was a significant positive correlation between baseline Kicer and subsequent improvement in PANSS positive (rho =0.64) and negative (rho=0.5) symptoms. Glutamate levels were not related to subsequent treatment response in the prospective cohort but were elevated in treatment resistant patients relative to responders in the cross-sectional cohort. The effect of low dose apomorphine was significantly related to baseline dopamine synthesis capacity. Conclusions Elevated dopamine synthesis capacity is associated with psychosis across diagnostic boundaries and linked to subsequent treatment response to dopamine blocking drugs. Glutamate alterations may only become manifest with long-term treatment. The potential for targeting the regulation of dopamine synthesis capacity is likely to depend on the initial state of the system. Funding MRC and Wellcome Trust. No industry funding received for the studies reported here.

A01

This abstract was withdrawn 10/07/17

A02

INVESTIGATING THE EFFECTS OF GENDER ON ANXIETY-RELATED BEHAVIOUR EVOKED BY KAPPA OPIOID RECEPTOR ACTIVATION IN THE ELEVATED PLUS MAZE

Lalji HM, Pharmacy and Pharmacology, University of Bath, Woodland Court W4D2 University of Bath, Bath. BA2 7PD hasnain2015@hotmail.co.uk

Bailey SJ(1), Bailey CP(1), Almatroudi A(1)

(1) As presenting author

Gender has been shown to be a factor in the pharmacological response to opiate analgesics. There is growing understanding that sex differences in the endogenous kappa opioid receptor (KOR) system could play a role in the development of drug dependence, depression and anxiety (Chartoff EH, Mavrikaki M. Front Neurosci. 2015;9:466). For example, the role of KORs in motivated behaviour of rats has been shown to have sex-dependent differences (Russell et al. Biol Psychiatry. 2014 Aug 1; 76(3): 213–222.) Here we have investigated the effects of the KOR agonist, U50,488 on behaviours in the elevated plus maze in CD1 mice of both genders. Adult male and female CD1 mice (8-10 weeks) were housed in groups of 4 .Male and female mice received either saline (0.9% w/v) or U50,488 5 mg/kg (s.c., 10 ml/kg, n=7 per group). Anxiety-related behaviour was assessed in a 5 minute elevated plus maze test, with open-arm light intensity at 150 lux and closed arms < 1 lux. Photobeam breaks were used to track behaviour using MotorMonitor

software (Campden Instruments). Two way ANOVA was used to assess the effects of treatment and gender (InVivoStat). U50,488 (5mg/kg) had no significant effect on the anxiety-related behaviour of female mice in the elevated plus maze. In male mice however, there was a significant increase in the amount of time spent in the open arms of the maze (Treatment effect; $F=5.49$, $p=0.0282$) although there was no effect on the distance travelled in the open arms. However, there was a significant reduction in total ambulations in the elevated plus maze in mice treated with U50,488, in both genders, compared to saline treated animals (Gender effect; $F=10.02$, $p=0.043$ and Treatment effect; $F=56.29$, $p<0.0001$). Taken together these results show that KOR activation elicits anxiolytic-like behaviour in males, with little or no significant effect on females. The total ambulation is decreased in both males and females which may be a significant confound of this study. A further important caveat is that we have only investigated a single dose of U50,488; it is possible that the dose-sensitivity of KOR to activation with U50,488 may be different between genders. Indeed at higher doses, 10mg/kg U50,488 has been shown to be anxiogenic, consistent with a role for KOR in stress-induced dynorphin release increasing anxiety-related behaviours. No Sponsorship was received for the study.

A03

STRESS-INDUCED ANXIETY IS NOT REVERSED BY HISTAMINERGIC PRECURSOR CHRONIC TREATMENT IN C57BL/6J MICE

Daher F, Lab of Neurosciences, CCBSFederal University of São Carlos, Rodovia Washington Luís, km 235 São Carlos SP, Brazil, 13565905 daher@usp.br

Padovan CM(2), Mattioli R(1)

(1) As presenting author; (2) Dept of Psychology, FFCLRP-Univ of São Paulo, Avenida Bandeirantes, 3900 Ribeirão Preto SP, Brazil 14040901

Introduction: Histaminergic neural system has been implicated in the mediation of emotional responses via receptors expressed throughout the brain. Histamine is a sensitive indicator of stressful experiences and modulates the activation of neuroendocrine stress response to influence defensive reactions (Haas et al. 2008, Physiological Reviews, 88, 1183-1241). Complementary, chronic exposure to stress, e.g. chronic unpredictable stress (CUS), induces long-term changes on affective, cognitive and physiological levels. However, little is known about the role of histamine on CUS model. Therefore, the present study investigated whether the histaminergic neurotransmission is involved on stress-induced anxiety. Methods: Male C57BL/6J mice (8 weeks old) were submitted (CUS, n=13) or not (Control, n=13) to CUS paradigm for 14 days and tested in the elevated plus maze (EPM). In a second experiment, L-histidine (LH; 500 mg/kg; via intraperitoneal – i.p.) or saline (SAL, 1ml/kg; i.p.) was administered to all animals (nLH=10; nSAL=10), 2 h after being stressed. Control mice received the same treatment and returned to their home cages (nLH=8; nSAL=9). On the 15th day, anxiety-like behavior was assessed using the EPM test. Mice were then anesthetized and transcardially perfused, with brains removed for c-Fos^{+} immunoassays (n=2/group). Number of enclosed arm entries (EAE) and percentage of entries (OAE) and time (OAT) in the open arms were analyzed by Student's t-test or two-way ANOVA, followed by Duncan's test ($p\leq0.05$). All procedures were approved by the Animal Research Ethics Committee (#044/2013). Results: In CUS mice, exposure to stress induced a significant reduction on %OAE ($T24=3.14$; $p<0.05$) and %OAT ($T24=2.03$; $p=0.05$) when compared to control, without changing EAE. Similar effects were observed in the second experiment, specifically for stress condition: SAL- and LH-stressed mice displayed decreased %OAE ($F1,33=4.07$; $p=0.05$) and %OAT ($F1,33=5.60$; $p<0.05$) when compared to non-stressed groups. No changes were observed on EAE. There was no significant interaction between stress and drug on %OAE ($F1,33=0.09$; $p>0.05$) and %OAT ($F1,33=0.02$; $p>0.05$). Preliminary data on c-Fos expression indicated a trend for increased amygdaloid complex activation in SAL-stressed (BLA: 26.84±0.15; La: 36.58±2.67; CeA: 55.04±3.53) and LH-control (BLA: 28.55±2.66; La: 40.31±8.28; CeA: 48.32±0.09) mice compared to SAL-control (BLA: 18.64±2.55; La: 31.80±1.88; CeA: 40.21±3.09) and LH-stressed (BLA: 21.32±1.08; La: 29.13±9.92; CeA: 40.40±9.18) groups. Conclusions: These evidences suggest that 2-week-long CUS regimen consistently induces anxiogenic-like response in adult male mice, which cannot be prevented by chronic treatment with LH. Also, preliminary results suggest differential activation of the amygdaloid complex associated to CUS and, potentially, to LH treatment. Financial support: FAPESP (2013/10761-9), CNPq (3030882014-1) and CAPES.

A04

ACTIVATION OF 5-HT7 RECEPTORS LOCALIZED IN THE MEDIAN RAPHE NUCLEUS ARE INVOLVED IN THE DISCONNECTION OF STRESSFUL MEMORIES IN RATS

Padovan CM, Psychology, University of São Paulo - FFCLRP, Av Bandeirantes, 3900, Cidade Universitária, 14040901, Ribeirão Preto, SP, Brazil, 14040901 cpadovan@usp.br

Lopes WL(1), Zuelli FMGC(1)

(1) 2 Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Avenida Bandeirantes 3900, 14040-900, Ribeirão Preto, SP, Brazil.

Animal models associated to uncontrollable stress have been widely used to investigate the mechanisms underlying mood disorders. Serotoninergic agents such as antidepressants have been shown to attenuate and/or prevent the consequences of exposure to stress. More recently, it has been proposed that 5HT7 receptor antagonists have antidepressant properties, however, the brain sites underlying such effects are not fully understood. 5HT7 is expressed in the hippocampus and median raphe nucleus, and these brain structures have been proposed to be the main serotoninergic pathway underlying disconnection of stressful memories. Therefore, the aim of this work was to investigate the role of MnRN 5-HT7 submitted to the Forced Swim Test. All procedures were approved by the Animal Research Ethics Committee (#2014.1.231.53.9). Male wistar rats (7 weeks old) with a cannula aimed to the Median Raphe Nucleus were used. LP-44 (LP; 5HT7 agonist; 0.3 nmol/0.2µl), SB 258741 (SB; 5HT7 antagonist; 0.1 nmol/0.2µl) and/or Saline (SAL; 0.2µl) were administered as follows: SAL+SAL(n=10-13), SAL+LP(n=9-12); SB+SAL(n=8-12) and SB+LP(n=9-11). Intra-MnRn treatment was performed immediately before or after exposure to a 15min forced swim session (FSS), or 24h after this pre-exposure. Test consisted of a 5 min swim session during which the following behaviours were recorded for further analysis: latency to display immobility (LAT) and total time spent immobile (TSI). Frequency and total time of climbing (FC and TC) and diving (FD and TD) are current under analysis. Control experimental conditions included intra-MnRN treatment 24h or 5min before test. After test rats were sacrificed under anaesthesia, transcardially perfused and had their brain removed for histological analysis of the injection site. Data was analysed by ONEWAY ANOVA followed by Duncan test, considering significant $p<0.05$. Intra-MnRN LP increased LAT when administered before SS ($F3,36=13.31$; $p<0.05$) and before test ($F3,41=10.21$; $p<0.05$), but not when given after SS ($F3,41=0.085$; $p>0.05$). Similarly, LP did decrease TTI when given before ($F3,36=8.61$; $p<0.05$), after ($F3,41=5.92$; $p<0.05$) or previous to the test ($F3,41=12.7$; $p<0.05$). These effects were prevented by previous treatment with SB. In control experimental conditions.no differences were observed between groups on the LAT (24h: $F3,39=2.05$; $p>0.05$; 5min: $F3,32=0.33$; $p>0.05$) or TTI (24h: $F3,39=0.84$; $p>0.05$; 5min: $F3,32=0.98$; $p>0.05$). Our data suggest that activation of MnRN 5HT7 are important for the disconnection of stressful memories, thus allowing adaptation to stress. Financial Support: FAPESP (2014/20837-5; 2014/26753-8; 2013/20175-0).

A05

CACNA1C DYSFUNCTION: THE IMPACT ON ADULT NEUROGENESIS

Moon AL, DPMCN, Cardiff University, Hadyn Ellis Building Maindy Road Cardiff CF24 4HQ, CF24 4HQ moonal@cardiff.ac.uk

Hall J(1), Thomas KL(1), Brydges N(1), Haan N(1)

(1) As presenting author;

Introduction Genome-wide association studies have consistently demonstrated that variation in the gene calcium voltage-gated channel subunit alpha1C (CACNA1C) increases risk for psychiatric disorders. CACNA1C encodes the Cav1.2 subunit of voltage-gated calcium channels (VGCCs), which have been functionally implicated in a broad spectrum of neuropsychiatric syndromes. VGCCs have been shown to facilitate neural precursor differentiation and there is some evidence that disruption of Cav1.2 leads to dysfunction of adult hippocampal neurogenesis, which may be a key contributor to the cognitive impairments in psychiatric disorders. Since parvalbumin (PV)-containing interneurons play a role in regulating adult neurogenesis and depend on VGCCs for normal development, we hypothesised that they mediate impairments in neurogenesis following disruption of CACNA1C. The aim of this research is to

assess any alterations to components of adult neurogenesis in Cacna1c heterozygote (Cacna1c +/-) rats and the subsequent impact on behaviour. Methods The dentate gyri of male Cacna1c +/- rats (n = 8/genotype) were examined for the neurogenic markers doublecortin (DCX) and 5-bromo-2-deoxyuridine (BrdU), and also PV. Cacna1c +/- rats and their wild-type littermates were subjected to trace (n = 8/genotype, males only) and delay (n=8/genotype, males only) auditory fear conditioning paradigms, and tested for conditioned responses by assessing context or cue-elicited freezing in recall sessions. Results Cacna1c +/- rats showed a 50% decrease in the neurogenic cell proliferation marker BrdU compared to wildtype animals ($p = 0.039$). However, there was no change in doublecortin ($p = 0.84$). There was also a significant decrease in PV in the dentate gyrus ($p = 0.0074$). Cacna1c +/- rats subjected to trace fear conditioning showed increased freezing to cue ($p = 0.0257$), whereas those subjected to delay fear conditioning showed increased contextual freezing in comparison to wild-types ($p = 0.0331$). Conclusions Dysfunction in the Cacna1c gene leads to decreased cell proliferation in adult neurogenesis. This deficit may be due to PV-containing interneuron dysfunction. However, there is no difference in total immature neurons, suggesting that a lack of apoptosis may compensate. Cacna1c disruption impairs associative trace conditioning to cue. Since trace conditioning requires hippocampal neurogenesis to support appropriate associative learning, these results suggest that deficits in cell proliferation in Cacna1c +/- rats may result in impairment of associative trace fear. Finally, it is notable that Cacna1c +/- rats also showed increased contextual fear to the amygdala-associated delay conditioning, suggesting these rats may have a general deficit in forming correct associations and buffering against the nonassociative, anxiogenic effects of fear conditioning. This study was sponsored by funding from the MRC, as part of a PhD grant/stipend.

A06

NEURODEVELOPMENTAL AND BEHAVIOURAL CONSEQUENCES OF MATERNAL IMMUNE ACTIVATION IN MALE AND FEMALE WISTAR RATS

Oladipo JM, Division of Pharmacy and Optometry University of Manchester, University of Manchester, Stopford Building Room 2.128, Oxford Rd, Manchester, M13 9PT joanna.oladipo@manchester.ac.uk

Fasolino V(1), Edye ME(2), Doostdar N(1), Podda G(1), Manca M(1), Miyan J(1), Neill JC(1)

(1) Division of Pharmacy and Optometry, Faculty of Medicine, Biology and Health, University of Manchester, Oxford Rd, Manchester M13 9PT; (2) Neurorestoration Group, Wolfson CARD, King's College London, Guy's Campus, London SE1 1UL

Background: Viral infection during pregnancy is suggested as a risk for the development of autistic spectrum disorder (ASD). Maternal immune activation (mIA), using the viral mimetic poly(I:C), produces phenotypes relevant to ASD in mice when administered at gestational day (GD)12.5. However, no studies have explored mIA at GD12.5 in rats. Our aim is to characterise effects of mIA at GD12.5 on offspring neurobiology and behaviour in Wistar rats. Methods: Pregnant female Wistar rats were injected (i.p.) with poly(I:C) (10mg/kg, n=15 dams) or saline (n=18 dams) at GD12.5. Male and female offspring were monitored for changes in morphometric parameters at GD21 (n=36-51 pups/treatment), (body weight (BW), brain weight (BrW) and placental weight (PW). Postnatally, BW was measured regularly until postnatal day (PD)21 alongside BrW (n=22-30 pups/treatment). Analysis of anxiety-like and repetitive behaviour was conducted in adolescence (n=12-16 pups/treatment) using the open field test (OFT). Gene expression in frontal cortex (FC) of GD and PD21 offspring was measured using qPCR for genes related to synaptic development and stability (Snap25, PSD95 and Shank3) as well as stability of the blood brain barrier (BBB) (Mfsd2a). For data analysis between treatment groups, a nested-ANOVA was used with litter as a random variable. Results: At GD21, no effect of mIA was observed on BW or BrW. In male offspring only a significant down regulation of Snap25 gene expression in the FC was found ($p<0.05$). A significant reduction was found in female PW ($p<0.01$) and at PD1 in BW for both sexes from poly(I:C) dams vs. saline ($p<0.001$). Reduced BW was maintained at PD12-21 ($p<0.001$). BrW from offspring at PD21 was decreased in male offspring from poly(I:C) dams vs. saline ($p<0.01$). A significant increase in the expression of Shank3 was found in FC of male offspring only ($p<0.05$). In females, a significant reduction in expression of BBB integrity marker Mfsd2a was shown in the FC ($p<0.05$). Similarly, only male offspring showed a significant increase in anxiety-like behaviour in the OFT ($p<0.05$). Both male and female offspring from poly(I:C) dams showed increased grooming in the OFT that failed to reach statistical significance. Conclusion: To

our knowledge this is the first mIA study investigating the effects of 10mg/kg poly(I:C) in Wistar rats at GD12.5. We provide an in depth developmental analysis of both male and female offspring in this model. mIA resulted in sex specific alterations in morphometric parameters and gene expression in the FC at PD21. A decrease in BrW at PD21 may indicate a disruption to synaptic growth during development. A subtle behavioural phenotype relevant to ASD was shown by only male offspring. Further validation of this model is underway to explore effects on gene and subsequent protein expression related to synaptic development and other brain markers relevant to ASD. No sponsorship was received for this study.

A07

GLUCOCORTICOID RECEPTOR AND ITS MODULATOR FKBP51 MRNA EXPRESSIONS ARE DOWNREGULATED IN AN EXPERIMENTAL MODEL OF EARLY-LIFE ADVERSITY ASSOCIATED WITH PSYCHOPATHOLOGIES.

Juruena MF, Psych Med, Centre for Affective Disorders, IoPPN, KCL, Room E2.08 PO72, De Crespigny Park Denmark Hill, London, SE5 8AF mario.juruena@kcl.ac.uk

Umeoka E(1), Umeoka MSS(2), Antunes-Rodrigues J(3), Garcia-Cairasco N(3), Mello MF(4)

(1) Dept of Neuroscience and Behavioral, FMRP, University of Sao Paulo; (2) Dept Physiology, FMRP, University of Sao Paulo; (3) Dept Physiology, FMRP, University of Sao Paulo; (4) Dept Psychiatry and Psych Med, Federal University of Sao Paulo;

Early life adversities have constantly been associated with increased risk for development of psychopathologies later in life, and the hypothalamus-pituitary-adrenal axis malfunctioning seems to be the link between stress early in life and brain disorders such as major depression and bipolar disorder, among others. A translational approach is a keen strategy in the search for new insights into the mechanisms behind this phenomenon; in this regard we evaluated the expression of glucocorticoid receptor (GR) and one of its modulators FK506 binding protein 51 (FKBP51) in brain tissue from C57BL6 mice subjected to an experimental paradigm of early-life stress from P2 to P9, which recently has been associated with psychiatry-like phenotypes. At P9, mice from control and stress groups were decapitated between 8:00 and 9:30 immediately after the body weights were determined. Blood samples for corticosterone assessment were taken, and the brains were quickly removed from the skull and stored for posterior dissection and RNA extraction. Corticosterone levels were determined by radioimmunoassay, and the brains were manually dissected to obtain a slice of tissue that included cortex, hippocampus, thalamus and hypothalamus. Total RNA was extracted and reverse transcripted to cDNA using Qiagen specific kits. Quantitative real-time PCR (qPCR) was conducted using QuantiNova SYBR Green PCR Reagents (Qiagen) in 96-well plates on a StepOne Plus Real-Time PCR System (Applied Biosystems) using universal cycling conditions. Relative quantification of gene expression was calculated using the CT2 method; the housekeeping gene (GAPDH) was used to normalise the expression of the target genes. Primers were acquired from IDT. Mice subjected to stress, compared to controls, presented significantly reduced body weight (2.75 ± 0.13 g, N=21 and 3.89 ± 0.09 g; N=33; Student T-test $p<0.001$) and increased corticosterone basal levels (5.41 ± 1.32 ug/dl, N=21 and 2.63 ± 0.18 ug/dl, N=26; Student T test $p=0.0258$). Moreover, stressed mice, compared to controls, showed significant lower expression of GR (0.35 ± 0.05, N=16 and 1.55 ± 0.24, N=31; Student T test $p=0.0012$) and FKBP51 (0.58 ± 0.08, N=15 and 1.14 ± 0.18, N=29; Student T test $p=0.03$). No significant differences were observed in the expression of Mineralocorticoid Receptor (MR) and Corticotrophin Releasing Hormone (CRH) mRNAs. Our findings indicate that early-life adversity promoted lower mRNAs expression of GR and FKBP51 whereas MR and CRH were not altered, pointing to an imbalance in this system. Ongoing behavioural and molecular experiments will provide further evidence on the role of GR and MR on psychiatry conditions related to poor life quality during childhood. Financial support from Academy Medical Sciences/Royal Society, FAPESP and FAEPA.

A08

THE IMPACT OF INDUCED AND UNMEDICATED PATHOLOGICAL ANXIETY ON A BACK-TRANSLATED MEASURE OF NEGATIVE BIAS.

Aylward J, ICN, UCL, 17 - 19 Queen Square, London, WC1N 3AZ, WC1N 3AZ j.aylward@ucl.ac.uk

Robinson OJ(1)

(1) As presenting author

Introduction The tendency to focus on negative stimuli at the expense of positive stimuli, so called 'negative affective bias', is implicated in the development and maintenance of anxiety disorders but the underlying neurobiology is unknown. Adopting the same paradigm across animal and human models can develop this full neurobiological understanding and, moreover, enable the successful screening of candidate novel anxiolytics. Here, we therefore explore the influence of pathological and induced anxiety in humans on a back-translated rodent assay of negative affective bias in the interpretation of ambiguous auditory cues (Hales et al., 2016, PLoS ONE 11(3): e0152592). Methods Our task design directly back-translated the animal paradigm. Firstly, participants learned to make correct responses to tones (500hz or 1000hz), which were associated with different reward amounts (£1 or £4; counterbalanced). In the main task they then responded to ambiguous tones (750hz), randomly associated with reward level. The proportion of low reward responses made to the ambiguous tone represented the degree of negative affective bias. An adapted drift diffusion model was also fitted to the reaction times to more precisely disambiguate the decision-making process underling bias. In study 1, this task was completed by unmedicated anxious (ANX; N=30) and healthy individuals (HC; N=47). In study 2, a within-subjects induced anxiety version was completed under alternating conditions in healthy controls (N = 47 participants at risk of, and safe from shock, respectively). Results In study 1, the ANX group demonstrated a significantly more negative bias ($t(75) = 3.08$, $p = 0.003$; BF10 = 12.51). Drift diffusion analysis suggested that this was driven by a slower drift rate in the ANX group ($t(75) = 2.70$, $p = 0.008$; BF10 = 5.22). In study 2, threat of shock induced increased self-reported anxiety ($t(44) = 8.92$, $p < 0.001$, BF10=19.97, but had no effect on negative bias (all $p > 0.05$, BF10 < 1). Conclusion Our results translate those in rodents undergoing anxiogenic manipulation, suggesting that this translational measure indexes negative affective bias in pathological anxiety but not transient anxiety in healthy controls. This demonstrates the translational potential of this paradigm in developing novel therapeutics and provides a potential means of ultimately understanding the neurobiology of negative affective bias in anxiety disorders. Given the importance of these biases in contributing to and maintaining anxiety disorders, as well as the failure of many preclinical to phase 1 clinical trials, such translational pipelines are of growing importance. Funded by an MRC Career Development Award to OJR (MR/K024280/1).

A09

USING AN ONLINE PERSONALITY QUESTIONNAIRE FOR RAPID RECRUITMENT OF HARD TO FIND PARTICIPANTS IN PHARMACOLOGICAL RESEARCH

Patrick F, Psychological Medicine, Institute of Psychiatry, Psychology & Neuroscience, 103 Denmark Hill, London, SE5 8AF fiona.patrick@kcl.ac.uk

Higgens-Stockden F(1), Young AH(1), Perkins AM(2)

(1) Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King; (2) National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and the Institute of Psychiatry, Psychology & Neuroscience, King

Introduction The Five Factor Model (FFM) of personality has been widely explored within both mental and physical health (Lahey, 2009/ American Psychologist/ 64/ 241); Krueger et al, 1996/ Journal of abnormal psychology/ 105/ 299). Vulnerability to a range of mental health disorders have been strongly linked to the FFM personality trait of neuroticism (Lahey, 2009). Providing an easy-access and affordable way of identifying intervention naïve individuals meeting the criteria for DSM diagnoses would be a boon to pharmacological research. Method We created an online personality questionnaire, adapted from the FFM-based Trait-State Description Inventory (TSDI; Collis & Elshaw, 1998/ TTCP/98-001). The questionnaire was

reduced to 50 items, in an attempt to prevent questionnaire fatigue whilst preserving the data quality. The questionnaire website was advertised via KCL student circular systems. Eligibility criteria were English language proficiency, access to the internet and being over 18 years old. Participants with neuroticism trait scores of > 1 standard deviation above the mean were invited to take part in a pharmacological study in generalised anxiety disorder (GAD). The path from personality test completion to study enrolment was investigated for efficacy. Results 4392 individuals completed the online questionnaire. The mean and distributional data is presented, alongside correlational information. Of these, 531 (12.1%) individuals met trait neuroticism criteria. 221 individuals contacted the researchers regarding participation in the second study. 164 responded to telephone screening, with 53 chosen for medical screening, with only 5 (9.3%) failing to meet the criteria for GAD when assessed in person using the MINI. Discussion This data indicates that informative data can be obtained via an online version of the TSDI, as well as showing that use of an online tool such as this could increase efficacy in screening of potential participants in studies investigating anxiety, and potentially mental health more broadly. This paradigm is suggested as a useful addition to research recruitment drives in the general population. This data was part of a study sponsored by Bionomics.

A10

SEROTONIN TRANSPORTER (SLC6A4) EXPRESSION IN THE RIGHT AMYGDALA AND SEROTONIN 2A AND 2C RECEPTOR EXPRESSION RATIO (HTR2A:2C) IN THE RIGHT AMYGDALA AND DORSAL ANTERIOR CINGULATE CORTEX (DACC) ASSOCIATES WITH ANXIOUS BEHAVIOUR

Quah SKL, Physiology, Development and Neuroscience, University of Cambridge, Innes Building Madingley Road Cambridge, CB3 0ES sklq2@cam.ac.uk

Santangelo AM(1), Roberts AC(1)

(1) As presenting author

Introduction Trait anxiety, which is the enduring disposition to feel stress and worry, has been proposed to confer increased vulnerability to developing anxiety disorders. Our lab found recently that high trait anxious marmosets show reduced extracellular serotonin levels in the amygdala, implicating an altered serotonin system in the expression of high trait anxiety (Mikheenko et al. 2015, Neuropsychopharmocology, 40(6):1395-404). In humans, trait anxiety has been associated with altered activity not only in the amygdala but also prefrontal and dorsal anterior cingulate circuitry. Since serotonin has been implicated in the balance of activity between these regions and the amygdala, the aim of this work is to identify differential expression of serotonergic genes within these brain regions that may be associated with anxious behaviour. Methods Target genes including the serotonin transporter (SLC6A4) and the serotonin 1A (HTR1A), 2A (HTR2A), and 2C receptors (HTR2C) were investigated in twelve common marmosets, Callithrix Jacchus (age: 3.82 ± 0.55 years; gender: 5 females and 7 males). Relative gene expression was obtained via quantitative real-time polymerase chain reaction from target brain regions, including the medial prefrontal, orbitofrontal, ventrolateral prefrontal and dorsal anterior cingulate (dACC), cortices, amygdala, dorsal and median raphe nuclei. Anxious behaviour was assessed using the human intruder test: the animal's behavioural response to an unknown human wearing a mask. The behavioural measures included vocalizations, average distance from the cage front, jumps to the front, head and body bobbings, and locomotion. A score for anxious behaviour was calculated via a principal component analysis (PCA) with oblique rotation (direct oblimin). Results Among all target brain regions, SLC6A4 expression was only correlated with anxious behaviour in the right amygdala ($r = .82$, $p = .001$). Serotonin 2A and 2C receptor expression ratio (HTR2A:2C) in the right amygdala ($r = .73$, $p = .007$) and both left ($r = -.682$, $p = .021$) and right ($r = -.762$, $p = .006$) dACC was also correlated with anxious behaviour. Conclusions Findings of higher serotonin transporter expression in the amygdala associated with anxious behaviour could help explain the phenomena of reduced extracellular serotonin in high anxious individuals and further supports the theory that low serotonin levels in the amygdala leads to high anxiety. The altered HTR2A:2C ratio within the amygdala and dACC in high anxious individuals emphasises the widespread influence of the serotonin system in anxiety and, in particular, the dACC-amygdala circuit (Robinson et al. 2014, The Lancet Psych, 1(4):294-302). Sponsors: MRC Programme grant MR/M023990/1(A.C.R.) and the Malaysian Public Service Department (PhD. Studentship, S.K.L.Q.).

A11

EVALUATING THE ANXIOLYTIC POTENTIAL OF IBUPROFEN IN THE 7.5% CARBON DIOXIDE EXPERIMENTAL MODEL OF ANXIETY

Barnes JW, Depts of Psychology & Psychiatry, University of Southampton, University of Southampton, SO17 1BJ m.j.garner@soton.ac.uk

Taylor ANW(1), Board A(1), Bell R(1), Hilton S(1), Mekhail I(1), Kok JJC(1), Baldwin DS(1), Garner M(1)

(1) As presenting author

INTRODUCTION Inhalation of 7.5% carbon dioxide (CO2) induces subjective, autonomic and neurocognitive features of anxiety in healthy subjects (Garner et al., 2011, Neuropsychopharmacology 36:1557–1562). CO2 challenge is considered a translational model of anxiety with potential for testing putative anxiolytic compounds (Bailey et al., 2011, J Psychopharmacol. 25(9):1199–1206). Acid-sensing ion channels (ASIC) are implicated in a number of health conditions including pain, neurological disease and anxiety. Initial studies in animals suggest that drugs that increase or decrease ASIC activity (particularly ASIC1) lead to corresponding increases and decreases in anxious behavior, however the effects in human anxiety are unknown. Nonsteroidal anti-inflammatory drugs (NSAIDS) have been found to inhibit both the activity and the inflammation-induced expression of ASIC1. Inhibition occurs with relatively low affinity and within the range of therapeutic concentrations of NSAIDs. We tested whether the widely used NSAID ibuprofen can reduce subjective, autonomic and neuropsychological response to 7.5% CO2 challenge in healthy adults compared to placebo. METHODS 27 healthy volunteers were randomised to receive a single dose of ibuprofen (400mg) or pill placebo (double-blind). Participants inhaled normal air for 20 minutes (control inhalation) before inhaling air enriched with 7.5% CO2 for 20 minutes (90 minutes post-drug to coincide with peak effects). During each inhalation participants completed an eye-tracking antisaccade attention task (Garner et al., 2011). Subjective anxiety (modified GAD-7), heart rate and blood pressure were recorded at baseline and after each inhalation. RESULTS Mixed-design analysis of variance (ANOVA) tested the effect of drug and inhalation gas on subjective and autonomic outcome measures. CO2 significantly increased heart rate and systolic blood pressure similarly in both drug and placebo groups. CO2-challenge increased subjective anxiety in both groups, however this effect was lower in the ibuprofen relative to placebo group ($F(1,25) = 3.21$, $p = .01$). CO2-challenge impaired attention control (increased erroneous eye-movement on antisaccade trials) irrespective of drug-group. CONCLUSIONS Our results provide some initial evidence that ibuprofen has anxiolytic effects in an experimental medicine model of human anxiety. Our findings invite further research into the ASIC and inflammatory mechanisms through which NSAIDs, including ibuprofen, might target anxiety and associated mood disorders. The study was approved by the University of Southampton Research Ethics and Governance Office. No funding was received for this study.

A12

FMRI INVESTIGATION OF THE EFFECT OF INDUCED ANXIETY ON PAVLOVIAN BIASES DURING REINFORCEMENT LEARNING IN HEALTHY AND ANXIOUS INDIVIDUALS

Goer FK, Institute of Cognitive Neuroscience, University College London, 17-19 Queen Square, London, WC1N 3AR franziska.goer@postgrad.manchester.ac.uk

Aylward J(1), Mkrtchian A(1), Roiser J(1), Robinson OJ(1)

(1) As presenting author

Introduction: Despite the high prevalence and cost of pathological anxiety, the underlying behavioural and neural mechanisms are not fully understood. Heightened reliance on innate Pavlovian cognitive biases, encouraging withdrawal in face of punishment, may underlie the harm avoidant behaviour observed in anxiety disorders during times of acute stress and thereby contribute to social withdrawal. Few studies to date have investigated the neural underpinnings of the effect of acute anxiety on interactions between Pavlovian biases and instrumental control. Moreover, it is unknown whether the underlying neural signature of these interactions under stress may differ in healthy controls (HC) and those with pathological anxiety (AN), an important distinction that may help elucidate observed behavioural differences. Methods:

The present study used functional Magnetic Resonance Imaging during a GoNoGo reinforcement-learning task under safe and threat of shock (ToS) conditions in HC (n=33) and AN (n=37). ToS is a well-validated method for inducing anxiety in a laboratory setting and benefits from a within-subject design that allows for comparison between states of acute anxiety (blocks when participants are at risk of unpredictable foot shocks) and safety (no shocks are administered). The GoNoGo reinforcement-learning task fully orthogonalises action and valence under threat and safe conditions, allowing for the comparison of trial types that are consistent with innate Pavlovian biases to those in which the instrumental instructions and the Pavlovian bias are in conflict. Results: Results revealed that threat differentially affected groups, with increased activation in the inferior frontal gyrus (IFG)/insula (xyz=-32, 28, 10,T= 4.03,p=.042 FWE SVC) during inhibition in AN but not HC, while decreased activation in the striatum(xyz=24, 12, 6, T= 4.15,p=.033 FWE SVC), during approach trials under threat was unique to AN. Conclusion: These findings suggest that AN participants may be particularly vulnerable to the effects of ToS induced withdrawal, as indicated by increased activation of inhibitory control regions (IFG/insula) during inhibitory trials in threat relative to safe conditions, as well as decreased activation of striatal regions crucial for action planning during approach trials under threat. Collectively this may indicate a neural signature of increased aversive Pavlovian biases in pathological anxiety during times of potential threat. This work was supported by Medical Research Council Career Development Award Grant No. MR/K024280/1 (to OJR).

A13

THE PSYCHOLOGICAL AND PHYSIOLOGICAL EFFECTS OF A NOVEL VIRTUAL REALITY STRESSOR.

Martens MAG, Psychiatry, University of Oxford, Neurosciences Building Warneford Hospital, OX3 7JX marieke.martens@psych.ox.ac.uk

Antley A(4), Pomes A(3), Slater M(2), Freeman D(4), Tunbridge EM(1), Harrison PJ(1)

(1) As presenting author; (2) Department of Computer Science, Malet Place Engineering Building, University College London, Gower Street, London WC1E 6BT; (3) EventLAB Universitat de Barcelona Facultat de Psicologia, Departament de Personalitat, Avaluació i Tractaments Psicològics, Campus de Mundet - Edifici Teatre, Passeig de la Vall d'Hebron 171, 08035 Barcelona Spain; (4) Univ Dept of Psychiatry, Warneford Hosp, Oxford OX3 7JX

The use of immersive virtual reality (VR) environments to assess psychiatric symptoms has great potential. Stress induces a range of physiological effects and is implicated in a number of psychiatric disorders. We investigated the physiological and psychological effects of a VR environment stressor. Non-smoking, healthy men (N = 24, 12 per group, mean age = 24.9 years, SD = 4.2) attended the VR-lab and, following a one-hour baseline period, were randomly assigned to either the control or stressor version of a VR lift environment. The control lift scenario consisted of a journey from the ground floor lobby up to the third floor; on arrival at the third floor, subjects were instructed to step out of the lift and tell the time on the clock in the lobby. The stress lift scenario consisted of a journey on an open platform from the ground floor up to the top of a skyscraper building, with an expanding view over the city. During this scenario, subjects would stand on a 3cm thick platform. Upon arriving at the top of the building subjects were instructed to step off the platform without hesitation (no plunge in case of falling). Physiological measures of arousal, including salivary-cortisol and - amylase, blood pressure and pulse, and skin conductance together with subjective stress ratings, assessed using visual analogue scales (VAS), were recorded at 20 minute intervals. Data were expressed and analysed as percentage change from baseline. Subjective stress ratings, blood pressure and pulse rate (monitored for 30 seconds) immediately after stepping out/off the lift were compared between the groups using t-tests or Mann-Whitney test as appropriate. Subjective rating of stress ($U=4$, $Z=-4.047$, $p<0.001$) and pulse ($U=22$, $Z=-2.708$, $p=0.007$), increased more in the stress condition than the control condition. There were no group differences in change of systolic ($t(21) = 0.879$, $p=0.389$) or diastolic ($t(21) = 1.359$, $p=0.189$) blood pressure. Analyses of salivary cortisol and amylase, skin conductance, and heart rate variability are ongoing. In summary, exposure to a VR stressor led to increases in pulse rate and subjective stress ratings, and suggests that VR may prove to be useful for studying the acute effects of drugs on the stress response. Our ongoing studies will compare the physiological and psychological effects with those observed with the Montreal Imaging Stress Task (MIST), an established experimental stressor. Work supported by MRC research grant (K013092) to PJH and EMT.

A14

NEUROMETABOLITES IN ANTERIOR CINGULATE CORTEX IN CHRONIC FATIGUE SYNDROME: A MAGNETIC RESONANCE SPECTROSCOPY STUDY AT 7 TESLA

Chen C, Department of Psychiatry, University of Oxford, Neurosciences Bldg, Univ Dept of Psychiatry, Warneford Hosp, Oxford OX3 7JX chi.chen@st-hughs.ox.ac.uk

Godlewska BR(1), Emir U(2), Angus B(3), Andersson M(3), Cowen PJ(1)

(1) As presenting author; (2) Nuffield Department of Clinical Neurosciences. Level 6, West Wing, John Radcliffe Hospital, Oxford OX3 9DU; (3) OUH NHS Foundation Trust, Department of Microbiology, JR Hospital, Oxford OX3 9DU

Introduction Chronic fatigue syndrome (CFS) is a disorder characterized by prolonged fatigue that cannot be explained by other established medical diagnosis. CFS patients also present with higher prevalence of mood disorder, cognitive dysfunction and autonomic nervous system (ANS) dysregulation. The anterior cingulate cortex (ACC) is involved in heterogeneous functions including cognitive/emotional behaviour and ANS regulation, which are highly relevant to the presentations of CFS. The aim of this study is to investigate the concentrations of neurometabolites, including glutamate, gamma-aminobutyric acid (GABA) and glutathione, in the ACC, using y magnetic resonance spectroscopy (MRS) at 7 Tesla (7T). Methods We studied 9 participants who met the Oxford criteria for CFS (Sharpe et al. Journal of the Royal Society of Medicine 84.2 (1991): 118.) and 17 healthy participants without any current or previous psychiatric disorder. Participants rated themselves on the Chalder Fatigue Questionnaire (CFQ) and Beck's Depression Inventory (BDI). All participant had a single proton (1H) MRS scan at the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Centre in Oxford. Scanning was performed on a 7T Siemens MAGNETOM scanner (Siemens, Erlangen, Germany) with a Nova Medical 32 channel receive array head coil. Spectra were measured from a voxel in the ACC (20 × 20 × 20 mm), Spectra were analysed with LCModel to obtain absolute concentrations of the neurochemicals. Differences between CFS and healthy participants were evaluated with independent t-tests. Results Participants with CFS had higher CFQ ($p< 0.001$) and BDI scores ($p=0.012$) compared to the healthy participants. The concentrations of GABA ($p=0.02$) and glutathione (GSH, $p=0.004$) in ACC were decreased by 25% and 27%, respectively, in CFS participants. Furthermore, levels of total N-acetylaspartate (tNAA, $p=0.018$) and the phosphocreatine/creatine pool (tCr, $p=0.023$) in ACC were decreased among the CFS participants. Discussion The present findings must be regarded as preliminary because of the small numbers of CFS participants. We found that the inhibitory neurotransmitter, GABA, and an antioxidant, GSH, were decreased while the indicators for neuronal viability (tNAA) and energy metabolism (tCr) were decreased in ACC in participants with CFS. These findings could be partly explained by systemic inflammation of CFS and further support the sustained arousal model of CFS proposed by Wyller et al. (2009, Behavioral and Brain Functions, 5(1), 10). This study indicates that hyperactivity of the ACC could play a role in the pathophysiology of CFS. Financial sponsorship: This study was funded by an MRC programme grant to PJC.

A15

NEURAL SYSTEMS UNDERLYING ACTIVE AVOIDANCE BEHAVIOUR IN MAJOR DEPRESSION

Wise T, Centre for Affective Disorders, Department of Psychological Medicine, Institute of Psychiatry, Psychology & NeuroscienceInstitute of Psychology, Psychiatry and Neuroscience, King's College London, 103 Denmark Hill London, SE5 8AF toby.wise@kcl.ac.uk

Marwood L(1), Williams SCR(2), Cleare AJ(1), Perkins AM(1)

(1) As presenting author; (2) Department of Neuroimaging, Institute of Psychiatry, Psychology & Neuroscience, King's College London

Introduction Anxiety is a prominent symptom of major depression, but its biological basis remains poorly understood. In particular, it is unclear what neural systems underlie pathological avoidance of perceived threats. Here we used a validated task involving active avoidance of mild electric shocks, combined with fMRI, to explore whether abnormal function in circuits responsible for avoidance underlies these symptoms. Methods 18 individuals with major depression, in addition to 17 healthy controls, performed an in-scanner task involving using physical effort to avoid stimuli paired with mild electric shocks. Activity

during anticipation and avoidance of threats was explored and compared between groups (clusterwise threshold = < .05 FDR corrected). Results Anticipation of avoidable aversive stimuli was associated with significant activation in dorsal anterior cingulate cortex and striatum, while active avoidance of aversive stimuli was associated with activity in dorsal anterior cingulate cortex and insula. No differences in activation were observed between healthy controls and patients. Conclusions Our results suggest that the task used was effective in identifying neural systems involved in avoidance of aversive stimuli, and activated similar areas to previous studies of this behaviour. However the absence of significant differences in activation between patients and controls suggest that major depression is not associated with abnormal function in these networks. Future research should investigate the basis of passive avoidance in major depression. Funding This research was funded by a Medical Research Council (MRC)/ IoPPN Excellence PhD studentship to LM and departmental funds.

A16

BELIEF ABOUT TREATMENT ALLOCATION PREDICTS PLACEBO RESPONSE IN THE 7.5% CARBON DIOXIDE MODEL OF ANXIETY

Huneke NTM, Dept of Psychiatry, Univ of Southampton, Academic Centre, College Keep 4-12 Terminus Terrace Southampton, SO14 3DT n.huneke@soton.ac.uk

Bamford S(1), Baldwin DS(1), Garner M(1)

(1) As presenting author

Introduction: Placebo-controlled studies are necessary to test novel anxiolytic treatments, but placebo 'treatment' can also produce clinical improvement. The placebo response is thought to result from interactions between prior expectations and learning (Bendetti et al., 2011, Neuropsychopharmacology, 36: 339-354). A participant's 'belief' in whether they were allocated to active medication or placebo may be influenced by their expectations and experience of a clinical trial. We investigated whether belief correlates with the magnitude of the anxiolytic response to placebo in the 7.5% CO2 experimental medicine model of anxiety. Method: We pooled data from healthy volunteers randomised to the placebo arms of 2-week double-blind trials (n = 51, 27 males, mean age 22.9 years). On day 14, participants completed 20-minute inhalations of normal air and air enriched with 7.5% CO2 (CO2-challenge) in randomised order. We recorded heart rate, blood pressure and subjective measures of anxiety at baseline and after each inhalation. Following testing, participants recorded whether they thought they were taking drug or placebo, and their confidence in this decision, on two visual analogue scales. These measures were combined to produce a single interaction term we called 'belief'. Results: Mixed model ANOVAs showed that CO2-challenge significantly increased blood pressure and heart rate ($F's > 4.10$, $p < 0.05$), and subjective measures of peak anxiety, fearfulness, and worry ($F's > 35.1$, $p < 0.001$). Follow-up analyses examined whether belief could predict physiological and subjective responses to CO2-challenge. Linear regression analyses showed that belief significantly predicted peak fearfulness ($R2 = 0.063$, $F(1,47) = 3.08$, $\beta = -0.384$, $p < 0.05$) and worry ($R2 = 0.077$, $F(1,47) = 3.84$, $\beta = -0.443$, $p < 0.05$), but order of inhalation did not. Belief and order of inhalation were not associated with peak heart rate or blood pressure. Conclusions: Participants who believed they were receiving active medication experienced less subjective anxiety during CO2-challenge. Interestingly, there was no effect of belief on physiological measures of anxiety. More studies are needed to further understand the link between participants' beliefs about drug group allocation and response in experimental medicine studies and clinical trials. MRC research grant MR/J011754/1 awarded to Garner & Baldwin. Huneke is an NIHR Academic Clinical Fellow with a supportive grant from the Research Management Committee of the Faculty of Medicine at the University of Southampton.

A17

CONCOMITANT PRESCRIPTIONS OF TRAMADOL OR PREGABALIN WITH ANTIDEPRESSANT DRUGS IN A PAIN SERVICE OUTPATIENT CLINIC: A RETROSPECTIVE CROSS-SECTIONAL CASE-NOTE STUDY.

Mutta E, Psychological Medicine, Southern Health NHS Foundation Trust, Southampton General Hospital, SO16 6YD ekta.mutta@southernhealth.nhs.uk

Miorelli A(1), Price C(3), Baldwin DS(2)

(1) As presenting author; (2) Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton; (3) University Hospital Southampton

Introduction: Pain services have a role in guiding clinical management of persistent distressing pain, including pharmacological treatment options. Concerns have been raised about the abuse potential of pregabalin, and about the co-prescription of the opioid analgesic tramadol (which also has serotonin-noradrenaline reuptake inhibitory properties) with certain antidepressants, with potential risks of serotonin syndrome and other adverse effects. We examined the extent of co-prescribing of tramadol with serotonergic antidepressants and prescription patterns for pregabalin among outpatients attending a local NHS pain service. Methods: Retrospective case-note survey of all patients referred between April-September 2016, data being gathered with a standardised pro forma, with examination of prescriptions, anxiety (GAD-7) and depressive (PHQ-9) symptoms, and degree of reported pain and quality of life (EuroQoL). Clinic letters to referring general practitioners (GPs) were examined to ascertain whether advice on co-prescribing conformed to NICE guidance. Results: Data were gathered for 351 individuals: GP letters were available in 328 (110 men, 218 women: age range 18-91 years), and comprehensive data were available for 297 (198 women, 99 men: mean age 51.83 yrs, age range 19-87 years). Concomitant prescriptions of tramadol and SSRI/SNRI antidepressants were found in 23 (7.74%) patients, and concomitant prescriptions of tramadol with amitriptyline or nortriptyline in 24 (8.08%) patients: no clinic letters to GPs contained advice about cautions or potential hazards when co-prescribing these medications. Prescriptions for pregabalin were found in 57 (16.84%) patients, the mean dosage being 311.6 mg/day. Anxiety and depressive symptom intensity was relatively low in the overall patient population (mean GAD-7 score 10.64 [SD 6.43], mean PHQ-9 score 13.54 [SD 7.14]), but higher in patients who were currently prescribed tramadol with an SSRI/SNRI (GAD-7 score 11.96 [SD 6.27], PHQ-9 mean score 16.96 [SD 6.71]) when compared to patients (n=40) who were taking tramadol alone (mean GAD-7score 10.03 [SD 6.30],mean PHQ-9 score 12.35 [SD 5.94]). Self-reported health status (scored 0-100) was generally unsatisfactory (mean score 40.89 [SD 22.69]): 56% of patients had ‘low health statuses (defined by a threshold score of 40 or less). Pregabalin prescriptions accorded with British National Formulary dosage recommendations in all patients: anxiety symptom severity was higher in patients prescribed pregabalin (GAD-7 mean score 11.78 [SD 6.3] than in patients not prescribed pregabalin (GAD-7 mean score 10.37 [SD 6.43]). Conclusions: We could find no evidence of inappropriately high dosage when prescribing pregabalin in this clinic sample. Tramadol was co-prescribed with an SSRI/SNRI antidepressant in only a minority of patients. Serial monitoring of anxiety and depressive symptom severity would inform prescribing decisions. There is scope to improve the extent of information conveyed between outpatient clinics and referring GPs. Funding: No funding was sought or obtained for this investigation.

A18

EFFECTS OF SSRIS ON PERIPHERAL INFLAMMATORY CYTOKINES IN PATIENTS WITH FIRST EPISODE GENERALISED ANXIETY DISORDER

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

Tang Z(2), Ye G(2), Chen X(2), Pan M(2), Fu J(2), Fu T(2), Liu Q(2), Gao Z(2), Baldwin SD(1)

(1) Department of Psychiatry, University of southampton, Academic Centre, College Keep, Southampton SO14 3DT; (2) Suzhou Psychiatric Hospital, Suzhou, Jiangsu, China;

Introduction: Research into psychoneuroimmunology has led to substantial advances in our understanding of the reciprocal interactions between the central nervous system and the immune system in neuropsychiatric disorders. To date, inflammation has been implicated in the pathogenesis of depression

and anxiety. The immunomodulating effects of antidepressants on depression have been reported, however, there is no evidence of the immunomodulating effects of antidepressants on anxiety. The aim of the study was to investigate the effects of SSRIs on peripheral inflammatory cytokines in patients with first episode generalized anxiety disorder (GAD). Methods: A prospective cohort design was employed: 42 Chinese patients with first episode GAD were recruited and they were treated with SSRIs for 12 weeks. All participants completed measures of anxiety using Generalized Anxiety Disorder 7-item (GAD-7) scale and the State-Trait Anxiety Inventory (STAI), pro-inflammatory cytokines using enzyme-linked immunosorbent assay (ELISA), and CRP determined by immunoturbidimetric method before and after SSRIs treatment. Results: Baseline measures of anxiety including both GAD-7 and STAI were significantly reduced ($p<0.01$). Baseline levels CRP and pro-inflammatory cytokines (including IL-1α, IL-2, IL-6, IL-8, IL-12, IFN-γ, and GM-CSF), were significantly reduced after treatment of SSRIs ($p<0.05$ in all cases). In addition, changes of anxiety measures co-vary with the changes of peripheral cytokine levels ($p<0.05$). Conclusions: This study is the first to investigate the effects of SSRIs on pro-inflammatory cytokines in Chinese patients with first episode GAD, which provides further support for the speculated link between inflammation and GAD. The study indicates moderate anti-inflammatory effects of SSRIs on GAD, and suggests that SSRIs may owe some of their therapeutic effect to their anti-inflammatory properties. Data from randomized controlled trials assessing anti-inflammatory effects of SSRIs is warranted in further larger studies. The study was funded by Suzhou Science and Technology Development Grant in China (Reference code SYSD2014132).

B01

MODULATING CATECHOLAMINERGIC NEURONS IN THE 5-CHOICE SERIAL REACTION TIME TASK USING DESIGNER RECEPTORS EXCLUSIVELY ACTIVATED BY DESIGNER DRUGS (DREADDS)

Fitzpatrick CF, Department of Drug Design and Pharmacology, Københavns Universitet Universitetsparken 2 2100 København Ø, 2100 ciaran.fitzpatrick@sund.ku.dk

Runegaard AH(2), Christiansen SH(2), Navntoft C(2), Woldbye DW(2), Gether U(2), Andreasen JT(1)

(1) As presenting author; (2) Department of Neuroscience & Pharmacology, University of Copenhagen

Introduction Attention deficit/hyperactivity disorder (ADHD) is a common neuropsychiatric disorder associated with inattention and impulsivity (Wilcutt, Neurotherapeutics, 2012, 9, 490-499). The pathophysiology of ADHD is unclear, but dopamine input from the ventral tegmental area (VTA) and noradrenaline input from the locus coeruleus (LC) to the nucleus and accumbens prefrontal cortex appear to be centrally involved in mediating both processes (Del Campo et al., 2011, Biol Psychiatry, 69, e145-157). To further determine the roles of both neurotransmitters, mice were tested in the 5-choice serial reaction time test (5-CSRTT) using the Designer Receptors Exclusively Activated by Designer Drugs (DREADD)-based chemogenetic tools (Roth, 2016, Neuron, 89, 683-694). Methods Once male TH-Cre mice reached 5-CSRTT asymptotic performance at a baseline, stimulus duration value of 1.5 s, mice were stereotaxically injected with a viral vector encoding inhibitory DREADDs (AAV8-hSyn-DIO-hM4Di-mCherry) into either the VTA (n=13) or LC (n=5) in order to exert selective, inhibitory control over catecholaminergic input. Mice were tested with clozapine N-oxide (CNO; 0.5, 1 and 2 mg/kg), the activating DREADDs ligand in the 5-CSRTT must touch and baseline stages. Results In the must touch stage, VTA DAergic neuronal inhibition resulted in reduced correct trials ($p<0.05$, 1 mg/kg CNO; $p<0.01$, 2 mg/kg CNO), mean correct ($p<0.05$, 2 mg/kg CNO) and reward collection latencies ($p<0.01$, 2 mg/kg CNO). VTA DREADD inhibition increased percentage omissions ($p<0.001$, 1 mg/kg CNO; $p<0.001$, 2 mg/kg CNO), while reducing number of trials completed ($p<0.05$, 1 mg/kg CNO; $p<0.01$, 2 mg/kg CNO), and reward collection latencies ($p<0.01$, 2 mg/kg CNO) in the baseline stage. Percentage premature responding was not affected by VTA DREADD inhibition. No effect of LC DREADD inhibition was seen in neither the must touch nor baseline stage. Conclusions These findings demonstrate that 5-CSRTT performance is dependent on DAergic drive from the VTA, particularly motivational drive. No effects of DREADD inhibition was found on impulsive action, questioning the hypothesis that aberrant DAergic signalling contributes to impulsiveness in ADHD. Projection-specific DREADD studies can help elucidate whether VTA DAergic neurons affect attentional performance. All testing procedures were in accordance with European Communities Council Directive of 24 November 1986 (86/609/EEC) and the Danish Animal Experimentation Act. Conflict of interest: None Financial Sponsorship: Lundbeck Foundation.

B02

EFFECTS OF AMPHETAMINE AND DOI ON IMPULSIVE ACTION IN THE 5-CHOICE SERIAL REACTION TIME TASK

Fitzpatrick CM, Department of Drug Design and Pharmacology, Københavns Universitet Universitetsparken 2 2100 København Ø, 2200 ciaran.fitzpatrick@sund.ku.dk

Maric VS(2), Andreasen JT(1)

(1) As presenting author; (2) Department of Neuroscience, Pomona College, Claremont, USA

Introduction: Impulsive deficits are found in a number of neuropsychiatric disorders such as attention-deficit/hyperactivity disorder and substance abuse (Dalley and Robbins, 2017, Nat Rev Neuroscim 18, 158-171). The 5-choice serial reaction time task (5-CSRTT) is a paradigm extensively used to assess attention and impulsive control in rodents (Robbins, 2002, Psychopharmacology, 163, 362-380). However, most 5-CSRTT studies do not typically account for the reduction in premature responding, the measure of impulsive action, upon repeated exposure of long or variable inter-trial interval (vITI) trial lengths (Sanchez-Rioge, 2012, Psychopharmacology, 219, 253-270). Methods: This study investigated the use of vITI (5, 10 or 15 s) probes across 15 consecutive sessions (twelve baseline and three drug sessions) to induce consistent premature responding levels across repeated 5-CSRTT sessions in 12 male C57BL/6J mice. Once mice habituated to the vITI schedule, the effects of amphetamine (AMPH) and (±)-2,5-dimethoxy-4-iodoamphetamine (DOI) were assayed in a Latin-square design experiment to determine whether pharmacologically-induced rises in impulsive action could be detected. Results: Mice habituated to the variable ITI schedule after only three sessions and showed consistently reliable premature responding levels until the end of the study. AMPH ($p<0.01$) and DOI ($p<0.05$) increased percentage premature responding at the 15 s ITI, while only DOI increased impulsive action at the 10 s ITI ($p<0.05$). DOI also increased the percentage omitted responses ($p<0.001$), mean correct latency ($p<0.01$), reward collection latency ($p<0.01$), and reduced total attempted trials ($p<0.001$) across drug sessions. Conclusion: This consecutively used, vITI schedule eliminated a confounding variable, i.e. repeated testing causes reduced impulsive action levels, which is not normally considered in 5-CSRTT studies. This approach demonstrated that mice habituated to this schedule after only three test sessions. In addition, both AMPH and DOI significantly enhanced impulsive action in mice. Utilization of such experimental design can help aid understanding of the neurobiological basis of impulsivity and drug discovery efforts in impulsive-associated psychiatric disorders. All testing procedures were in accordance with European Communities Council Directive of 24 November 1986 (86/609/EEC) and the Danish Animal Experimentation Act. Conflict of interest: None Financial Sponsorship: Lundbeck Foundation.

B03

ASSESSING ATTENTION & IMPULSIVITY IN A PUTATIVE MODEL OF ADHD

Fitzpatrick CF, Department of Drug Design and Pharmacology, Department of Drug Design and Pharmacology, Københavns Universitet Universitetsparken 2 2100 København Ø, 2100 ciaran.fitzpatrick@sund.ku.dk

Rickhag M(1), Gether U(1), McGirr J(2), Andreasen JT(2)

(1) Department of Neuroscience and Pharmacology, Molecular Neuropharmacology and Genetics Laboratory, Lundbeck Foundation Center for Biomembranes in Nanomedicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.; (2) As presenting author

Introduction Aberrant dopaminergic signalling is involved in numerous neuropsychiatric disorders, including attention-deficit/hyperactivity disorder (ADHD) (Swanson et al., 2007, Neuropsychol Rev, 17, 39-59). The dopamine transporter-triple alanine (DAT-AAA) knockin mouse strain contains a disrupted DAT PDZ (PSD-95/Discs-large/ZO-1) domain, resulting in 25% of wild type (WT) striatal DAT expression levels. The DAT-AAA strain also exhibits hyperlocomotion in novel environments and an attenuated response to amphetamine (Rickhag et al., 2011, Nat Commun, 4, 1580). The study aimed to assay the DAT-AAA strain in the 5-choice serial reaction time task (5-CSRTT), a test of visual attention and impulsive action. Methods Food-restricted male DAT-AAA mice (n=9) and WT littermates (n = 6), aged 8 weeks and 26-30 g when testing began, were trained to 5-CSRTT baseline of 2 s stimulus duration (SD). Then, mice were tested on a

variable intertrial interval (vITI) challenge (5, 10 and 15 s ITI) for 45 min across 15 consecutive sessions to assess impulsive action. Finally, DAT-AAA mice were tested on stimulus duration (vSD) (0.2, 0.4, 0.7, 1.1 and 1.8 s SD) challenge for one hour for two consecutive days to allow assessment of attention performance, visual processing speeds, visual thresholds and motor response baselines using Theory of Visual Attention (TVA) (Fitzpatrick et al., 2017, Psychopharmacology, 234, 845-855). Results No genotype differences in 5-CSRTT learning or acquisition was found. DAT-AAA exhibited significantly higher percentage premature responding in the vITI challenge at the 5 ($p<0.05$) and 15 ($p<0.05$) s ITI values, with near-significant effects occurring at the 10 ($p= 0.06$) s ITI probe. In the vSD challenge, DAT-AAA mice displayed reduced discriminative accuracy across all SD values ($p<0.01$), specifically at the 0.4 ($p<0.001$), 0.7 ($p<0.01$), and 1.1 ($p<0.5$) s probes. TVA modeling found that the DAT-AAA strain had significantly reduced visual processing speeds ($p<0.01$). Conclusions These findings show that reduced DAT expression is associated with enhanced impulsive action and impaired attentional performance in the 5-CSRTT. It appears that homeostatic levels of DAT and dopamine are necessary for optimal control of impulsivity and attentional function. Thus, the DAT-AAA mouse strain is a putative model of ADHD. Future pharmacological testing with conventional ADHD medications will assess the predictive validity of the DAT-AAA strain as an ADHD model. All testing procedures were in accordance with European Communities Council Directive of 24 November 1986 (86/609/EEC) and the Danish Animal Experimentation Act. Conflict of interest: None Financial Sponsorship: Lundbeck Foundation.

B04

EXPLORING CORTICAL DYSREGULATION OF GABAERGIC PATHWAYS IN THE PSYCHIATRIC ILLNESS-RELEVANT CYFIP1+/-KO MOUSE

Storan M, Neuroscience, Neuroscience and Mental Health Research Institute, University of Cardiff Neuroscience and Mental Health Research Institute Hadyn Ellis Building, Maindy Rd, Cardiff, CF24 4HQ ms2155@bath.ac.uk

Best C(1), Moon A(1), Hall J(1), Trent S(1)

(1) As presenting author

Introduction: Schizophrenia and Fragile X Syndrome (FXS) are neuropsychiatric disorders characterised by glutamatergic and gamma-aminobutyric acid (GABA) signalling imbalance. Cytoplasmic-FMRP-Interacting-Protein (CYFIP1) represents a highly penetrant risk gene for psychiatric disorders, and through its interaction with Fragile X Mental Retardation Protein (FMRP), can inhibit protein synthesis impinging GABA pathways (Tam et al., 2010, Biochem Soc Trans, 38(2), 445-51). GABA activates inhibitory post-synaptic ionotropic GABAA receptors (GABAARs) contributing to excitatory/inhibitory balance. Preclinical FXS studies (loss of Fmr1 gene) have revealed greater reduced GABAAR subunit expression within the cortex compared to the hippocampus and the prefrontal cortex (PFC) (D'Hulst et al., 2006, Brain Res, 1121(1), 238-45). Although the hippocampus and PFC are key brain regions involved in psychiatric disorders, the cortex is regarded to play critical roles in development, learning, perceptual grouping and attention, disrupted in disorders such as schizophrenia. Interestingly, despite the close biological interaction of FMRP and Cyfip1, it is unclear whether GABAergic dysregulation occurs in Cyfip1KO models. Recent work at Cardiff University (see Best et al., BAP poster, 2017) found increased expression of the GABAAR-delta subunit (Gabrd) in the hippocampus and PFC of male Cyfip1+/-KO mice. Here, we utilised Cyfip1+/-KO mice to explore whether dysregulation of GABAergic pathways in the Cyfip1KO model extends to the cortex. Methods: Brains were extracted from adult (3-4 months) male Cyfip1+/- heterozygous knockout mice (6NTac x JAX 6), alongside wild-type littermate controls (mice: n=9/10). Cortical regions were dissected and prepared for qPCR analysis. Gapdh and Hprt were housekeeper genes and gene expression fold change calculated via delta-delta Ct. Statistical comparisons used 1-way or 2-way (genotype x brain region) ANOVAs with Shapiro-Wilk normality tests. Complementary techniques included in situ hybridisation and western blotting. Results: Decreased Cyfip1 expression in Cyfip1+/-KO mice was equal across all 3 brain regions studied (Genotype x Brain region interaction: $F(2,51)=1.098$, $P=0.3413$; 2-way ANOVA). However, Gabrd expression was reduced in the cortex (12% decrease); in contrast to increases in the hippocampus and PFC (74% and 75%, respectively), resulting in a genotype x brain region interaction ($F(2,49)=3.741$, $P=0.03$). No further changes were observed for the tested synaptic GABAAR subunit Gabra1

and pre-synaptic enzyme Gad1 in the cortex. Conclusion: Here we show decreased Gabrd expression in the cortex (17%) of Cyfip1+/-KO mice. This finding matches Fmr1 KO literature and interestingly, is the direct opposite of increased expression in hippocampus and the PFC. Future work will further characterise the GABAergic components dysregulated in this genetic model including Gabra4 and Gabra5. Wellcome Trust Strategic Award (DEFINE), NMHRI Internal Funding, NARSAD Grant (Brain and Behavior Research Foundation).

B05

ADHD AND STIMULANT MEDICATION DISRUPT THE TEMPORAL LAG STRUCTURE WITHIN DEFAULT MODE AND SALIENCE NETWORKS

Clarke CL, Department of Neuroscience, Brighton and Sussex Medical School, Trafford Centre, Eastern Ring Road Falmer, Brighton, BN1 9RY c.clarke@bsms.ac.uk

Sethi A(2), Cercignani M(1), Harrison NA(1)

(1) As presenting author; (2) Clinical, Edu & Hlth Psychology, Div of Psychology & Lang Sciences, University College London, Gower Street, London, WC1E 6BT

Introduction Aetiological models of neurodevelopmental disorders such as ADHD have shifted focus from regional brain abnormalities to dysfunction within distributed brain networks. To date these have almost exclusively focussed on zero-lag synchronicity of brain activity and neglected substantial temporal structure within resting-state fMRI (rs-fMRI). Here we use a novel lag-thread analysis (Mitra et al., 2015 PNAS 112 (E2235-44)) to characterise effects of ADHD and stimulant medication on the temporal propagation of resting-state activity across the brain. Methods Thirty ADHD patients (mean 33.7±9.5 years, 19 male) and 30 (mean 32.6±9.5 years, 19 male) age- (p=0.66), IQ- (ADHD: 109.0±6.57, controls: 110.1±7.06, p=0.53) and sex-matched controls underwent rs-fMRI scanning twice (90 minutes after placebo/stimulant medication) in a double-blind study design. All completed a battery of questionnaires/cognitive tasks including Conners, Tridimensional Personality Questionnaire and delay-discounting. rs-fMRI was acquired on a Siemens 1.5T Avanto using a multi-echo sequence then pre-processed using Multi-Echo Independent Component Analysis (MEICA, Kundu et al., 2011 NeuroImage 60 (1759-70)) to remove non-bold-like components associated with movement and physiological artifacts. We found the time-delays required to maximise correlations between the time-series' of voxels across the brain. Decomposing this resultant time-delay matrix with principal component analysis (PCA) identifies independent 'lag-threads' of signal propagation across the brain. Results are reported at whole brain corrected thresholds. Results We first replicated previous findings of approximately 8 independent temporospatial sequences of activity that propagate across the brain. Similar to Mitra et al. these included 'lag threads' originating in brain stem and higher-order cortical regions. Interestingly, stimulant medication selectively altered lag within the anterior cingulate cortex (ACC), slowing this region's time of activation by mean (±s.e.) 0.34±0.08s compared to all other brain areas ($p<0.01$). In contrast, ADHD was associated with significantly quicker (mean 0.36±0.07s) recruitment of the precuneous compared to other brain regions ($p<0.05$). Mean lag in this region additionally predicted the inattention subscale score of the Conners. Conclusions Lag threads capture the temporal propagation of activity across the brain and are believed to underlie the anatomical structure of brain networks observed in resting-state fMRI. We observe significant shifts in lag thread structure in ADHD (that correlate with inattention severity) and after methylphenidate. Further relationships with ADHD symptom profiles and relevance for conventional rs-fMRI findings will be discussed. Funding: BSMS and Sussex Sackler Centre.

B06

DOPAMINERGIC MODULATION OF COGNITION IN ADULTS WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD)

Hook RH, Psychiatry, University of Cambridge, Herchel Smith Building for Brain and Mind Sciences Forvie Site Robinson Way Cambridge Biomedical Campus Cambridge, CB2 0SZ rwh29@medschl.cam.ac.uk

Muller U(1), Ioannidis K(3), Isobe M(2), Grant J(6), Chamberlain SR(4), Myklebust S(5)

(1) Adult ADHD Service, Barnet, Enfield and Haringey Mental Health NHS Trust, London, HA8 0AD;

Department of Psychiatry, University of Cambridge, Cambridge, CB2 0SZ; (2) As presenting author; (3) Cambridgeshire and Peterborough NHS Foundation Trust, Fulbourn Hospital, Cambridge, CB21 5EF; University of Cambridge, Addenbrooke's Hospital, CB2 0SZ; (4) Department of Psychiatry, University of Cambridge, Herchel Smith Building for Brain and Mind Sciences, Cambridge, CB2 0SZ; Cambridge and Peterborough NHS Foundation Trust, Fulbourn Hospital, Cambridge, CB21 5EF; (5) John Van Geest Centre for Brain Repair, University of Cambridge, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 OPY; (6) University of Chicago, Pritzker School of Medicine, Chicago, IL 60637

Attention-Deficit Hyperactivity Disorder (ADHD) is a prevalent and debilitating condition of childhood onset, associated with deficits across multiple cognitive domains including decision making (Mowinckel et al., 2015, Journal of Attention Disorders, 19(5), pp355-367). Psychostimulant medication represents a first-line treatment option for adult ADHD, but this class of medication is not always tolerated by patients, and may have addictive potential (due to effects on striatal dopamine) (Chamberlain et al., 2009, Biological Psychiatry, 65(7), pp550-555). Catechol-O-Methyltransferase (COMT) is the enzyme largely responsible for the inactivation of synaptic dopamine in the frontal lobes (Tunbridge et al., 2004, The Journal of Neuroscience, 24(23), 5331-5335). Tolcapone is a COMT inhibitor that has shown benefit in improving executive functioning in healthy volunteers (Apud et al., 2007, Neuropsychopharmacology 32(17063156) 1011-1020; Farrell et al., 2012, Biological Psychiatry, 71(6), 538-544), and in gambling disorder (Grant et al., 2013, European Neuropsychopharmacology, 23(11), 1587-1596). The aim of this pilot study was to evaluate the cognitive effects of single-dose tolcapone in adults with ADHD. 11 male participants with ADHD were entered into the study after providing informed consent and agreeing to abstain from any usual stimulant medication and caffeine before taking part. They received single dose of oral tolcapone (200mg) and placebo in a randomized, double-blind, cross-over design. On each visit, 1h after dosing (corresponding approximately to expected time of peak plasma levls), neuropsychological tests were completed including the Cambridge Gamble Task (CGT). Effects of tolcapone versus placebo on cognition were evaluated using repeated measures analysis of variance, controlling for drug order. There was a significant effect of tolcapone versus placebo on the proportion of points gambled on the CGT ($p=0.016$), such that participants gambled a lower proportion of points on drug. There was no significant interaction between drug condition and risk ratio, nor was there a main or interacting effect of drug order ($p>0.10$). These findings suggest that selective enhancement of cortical dopamine transmission using tolcapone may improve decision-making in ADHD. This may account for the beneficial symptomatic effects previously reported in gambling disorder. Future work will expand the sample size and explore a broader range of neurocognitive domains, and will also evaluate whether peripheral biomarkers (e.g. expression of dopamine receptors on peripheral blood cells) are predictive of the degree of cognitive improvement observed. This research was supported by a grant from the Wellcome Trust to Dr Chamberlain.

B07

THE NEUROFUNCTIONAL CORRELATES OF TIME DISCRIMINATION IN YOUNG ADULTS WITH AUTISM SPECTRUM DISORDER, ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND THE COMORBID CONDITION

Lukito S, King's College London, Institute of Psychiatry, Psychology and Neuroscience., King's College London Institute of Psychiatry, Psychology and Neuroscience Department of Child and Adolescent Psychiatry (PO85) 16 De Crespigny Park London SE5 8AF steve.s.lukito@kcl.ac.uk

O'Daly O(2), Lythgoe DJ(2), Whitwell S(3), Debnam A(3), Simonoff E(1), Rubia K(1)

(1) As presenting author; (2) King's College London, Centre for Neuroimaging Sciences; (3) The Adult Attention-Deficit/Hyperactivity Disorder (ADHD) and Autism National Service, Behavioural and Developmental Psychiatry Clinical Academic Group, South London and Maudsley Foundation NHS Trust

Introduction: Attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) often co-occur and share neurocognitive deficits. One such shared impairment is in sub-second time discrimination, frequently found in people with ADHD and some people with ASD (Falter & Noreika, 2014, Subjective Time, MIT Press, p. 557-598). No fMRI studies, however, have investigated these difficulties in adults with ASD and ADHD. Furthermore, it is unclear to what extent the comorbid disorder (i.e.,

ASD+ADHD) is similar or different from the pure disorders (i.e., ASD or ADHD) in the neurofunctional correlates of this function. Methods: We compared the neurofunctional correlates of the performance of a duration discrimination task (Hart et al., 2014, Journal of the American Academy of Child & Adolescent Psychiatry, 53(5), p.569-578) in young adult males with ASD (n = 23), ADHD (n = 25), ASD+ADHD (n = 24) and typical development (TD, n = 26) using functional magnetic resonance imaging (fMRI). Between-group effects were investigated in brain regions typically impaired in boys with ADHD, within spherical regions of interest (ROIs) with radius 10mm centred at peak coordinates in the lateral and dorsomedial prefrontal cortices, inferior parietal lobe, striatum and cerebellum reported in previous studies. A univariate ANOVA, co-varying total head movement, and post-hoc t-tests for assessing pairwise group differences were conducted using statistical parametric mapping (SPM8). Only ROIs showing significant or trend-level group effect at peak threshold of $p < .05$, family-wise error corrected, are reported. Results: The ASD+ADHD group demonstrated disorder-specific under-activation in right inferior frontal cortex (IFC) during duration discrimination compared to the ASD, ADHD and TD controls (all ps <= .017). The comorbid group also showed less activation in left cerebellum compared to the pure disorder groups (both ps <= .049). Under-activation in right dorsolateral prefrontal cortex (dlPFC) was shared in all clinical groups relative to TD (all ps <= .045). Conclusions: The disorder groups shared neurofunctional impairments in dorsolateral prefrontal cortex, a key region mediating working memory and attention. However, only the ASD+ADHD group demonstrated disorder-specific impairments in inferior frontal and cerebellar areas that are key for time discrimination. The findings show that the comorbid group has more severe impairments compared to the pure groups. Furthermore, given that these regions are typically impaired during time discrimination in boys with ADHD, the finding could potentially suggest that the comorbid group has more persistent neurofunctional impairments compared to the pure disorder form. Funding acknowledgement: This study was supported by the National Institute for Health Research (NIHR) Maudsley Biomedical Research Centre (BRC) for Mental Health at South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, Psychology and Neuroscience, King's College London. Steve Lukito received funding from the UK Medical Research Council (MRC) and Institute of Psychiatry, Psychology and Neuroscience PhD Excellence awards.

B08

DEFAULT MODE NETWORK CONNECTIVITY IN ADOLESCENTS WITH CONDUCT DISORDER AND VARYING LEVELS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER SYMPTOMS

Broulidakis MJ, Department of Psychiatry, University of Southampton, 4-12 Terminus Terrace, Southampton, SO14 3DT mjb1m17@soton.ac.uk

Fairchild G(3), Sully K(1), Blumensath T(5), Darekar A(2), Sonuga-Barke EJ(4)

(1) As presenting author; (2) Department of Medical Physics and Bioengineering, University Hospital Southampton NHS Foundation Trust, SO16 6YD; (3) Department of Psychology, University of Bath, Claverton Down, BA2 7AH; (4) Institute of Psychiatry, Denmark Hill, SE5 9RJ; (5) Institute of Sound and Vibration Research, University of Southampton, SO17 1BJ

Introduction: Conduct disorder (CD) is characterized by impulsive, aggressive and antisocial behaviors that may be related to deficits in empathy and moral reasoning. The brain's default mode network (DMN) has been implicated in self-referential cognitive processes of this kind. Method: We examined connectivity between key nodes of the DMN in 29 male adolescents with CD and 29 age- and sex-matched typically-developing adolescents. We ensured that group differences in DMN connectivity were not explained by comorbidity with other disorders by systematically controlling for the effects of substance use disorders (SUDs), attention-deficit/hyperactivity disorder (ADHD) symptoms, psychopathic traits and other common mental health problems. Results: Only after adjusting for co-occurring ADHD symptoms, the CD group showed hypo-connectivity between core DMN regions relative to typically-developing controls (p(corr)= 0.03). ADHD symptoms themselves were associated with DMN hyper-connectivity (for all nodes p(corr) <0.05). There was no effect of psychopathic traits on DMN connectivity in the CD group and the key results were unchanged when controlling for SUDs and other common mental health problems. Conclusions:

Future research should directly investigate the possibility that the aberrant DMN connectivity observed in the current study contributes to CD-related deficits in empathy and moral reasoning, and examine self-referential cognitive processes in CD more generally. This work was funded from awards issued to Edmund J. S. Sonuga-Barke and Graeme Fairchild repectively.

B09

COMPUTERISED COGNITIVE REMEDIATION THERAPY IN ADULTS WITH ADHD: PRELIMINARY STUDY

Tomlinson A, Department of Psychiatry, University of Oxford, University of Oxford, Oxford, OX3 7JX anneka.tomlinson@gtc.ox.ac.uk

Baskind R(3), Johnson J(1), Neill JC(2)

(1) 5 Boroughs Partnership NHS Foundation Trust ; (2) Div of Pharmacy & Optometry, University of Manchester, Stopford Building, Manchester, M13 9PT; (3) Leeds and York Partnership NHS Foundation Trust

Introduction: Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder now known to persist into adulthood. ADHD involves deficits in a number of cognitive domains including attention, impulse control and a wide range of executive functions. Pharmacological treatment alone may not be adequate enough to remediate all of the neuropsychological deficits in ADHD; thus, it is vital that other treatments are developed to target such deficits. Cognitive remediation (CR) is a therapeutic approach that targets specific cognitive domains. CR therapy involves the engagement in a program or activity that aims to enhance cognitive skills and ability over a set period of time by methods of repetition and development. Aim: A preliminary interventional study to examine the efficacy of the computerised CR program (CiRcuiTs) for adults with ADHD currently stable on medication. Methods: All participants (n=39) included in the study met the adult ADHD DSM-IV diagnostic criteria, were currently stable on ADHD medication for at least 3 months and had no comorbid psychiatric conditions. All ADHD participants completed a full self-report Connors Adult ADHD Rating Scale, WEISS-Functional Impairment Rating Scale and five neurocognitive tasks using the Cambridge Automated Neuropsychological Test Battery (CANTAB). These measures were used to establish a baseline in symptom severity, cognition function and functional impairment. Participants then completed the CR course which was conducted using the computerised program CiRcuiTs. Each participant completed 4-8 hours per week for 8-12 weeks, which consisted of various exercises that targeted specific areas of cognition. Therapy sessions were conducted individually and were assisted by a trained therapist. Participants would also complete homework tasks remotely. The initial assessments were repeated within 10 days of completing the CiRcuiTs course. N=12 completed the full CiRcuiTs program and were included in analysis. Results: Data were analysed using the independent samples t-test. Significant positive changes in ADHD symptoms, impairments in functioning and sustained attention were found following completion of the CiRcuiTs course. Participants showed significant improvements in symptoms of inattention ($p<0.01$) and problems with self-concept ($p<0.05$) as measured by the Connors. Patients also displayed significant improvements in the rapid visual information processing CANTAB task ($p<0.001$), and specific areas of functional impairment as measured by the WEISS, including; activities of daily living ($p<0.05$) and learning and work ($p<0.05$). Conclusion: We have shown that a course of CR therapy (CiRcuiTs), when used in combination with medication, remediates symptoms of attention and improves impairments in functioning in daily living in adults with ADHD. Financial declaration: This work was funded as part of a PhD studentship by the University of Manchester.

B10

SHARED AND DISORDER-SPECIFIC NEUROCOMPUTATIONAL MECHANISMS OF DECISION-MAKING IN AUTISM SPECTRUM DISORDER AND OBSESSIVE-COMPULSIVE DISORDER

Carlisi CO, Child & Adolescent Psychiatry, IoPPN, KCL, 16 De Crespigny Park London, SE5 8AF christina.carlisi@kcl.ac.uk

Norman LJ(6), Murphy CM(1), Christakou A(2), Chantiluke K(1), Giampietro V(3), Simmons A(3), Brammer M(3), Murphy DM(5), Mataix-Cols D(4), Rubia K(1)

(1) As presenting author; (2) Centre for Integrative Neuroscience and Neurodynamics, University of Reading RG6 6AH; (3) Centre for Neuroimaging Sciences, IoPPN, KCL; (4) Department of Clinical Neuroscience, Karolinska Institutet Stockholm; (5) Forensic and Neurodevelopmental Sciences, IoPPN, KCL; (6) University of Michigan Dept of Psychiatry

Introduction: Autism spectrum disorder (ASD) and obsessive-compulsive disorder (OCD) are often comorbid and share phenotypes of repetitive behaviours, possibly underpinned by abnormal decision-making. However, no studies have compared the neural correlates of decision-making in these disorders. Methods: Brain-activation of boys with ASD (N=24), OCD (N=20) and typically-developing controls (N=20) during the Iowa Gambling Task was compared, and computational modelling compared performance. Results: Patients were unimpaired on number of risky decisions, but modelling showed that both patient groups had lower choice consistency and relied less on reinforcement learning compared to controls. ASD patients had disorder-specific choice perseverance abnormalities. Neurofunctionally, ASD and OCD boys shared left dorsolateral and right inferior frontal underactivation compared to controls during decision-making. During reward/loss outcome anticipation, patients shared underactivation in left lateral-inferior/orbitofrontal cortex and right ventral striatum. During reward receipt, ASD boys had disorder-specific enhanced activation in left inferior frontal/insular regions relative to OCD boys and controls. Conclusions: This study showed that ASD and OCD individuals use different decision-making strategies to perform comparably to controls. Patient groups showed shared abnormalities in lateral-(orbito)fronto-striatal circuitry linked to reward processing, but ASD boys had disorder-specific lateral inferior frontal/insular overactivation, suggesting that both shared and disorder-specific neurofunctional mechanisms underpin decision-making in these disorders. This work was supported by the Medical Research Council grants G0300155 to K.R. and the MRC UK Autism Imaging Multicentre Study G0400061 to D.M. This work represents independent research part-funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. K.C. and L.N. were supported by Ph.D. studentships from the Institute of Psychiatry, Psychology and Neuroscience, King's College London. C.C. was supported by a NIHR-BRC PhD studentship.

B11

USING WEARABLE SENSOR TECHNOLOGY TO MANAGE EBAD (EMOTIONAL, BEHAVIOURAL AND AUTONOMIC DYSREGULATION) IN PATIENTS WITH COMPLEX NEURODEVELOPMENT DISORDERS

Santosh PJ, Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, 16 De Crespigny Park, King's College London, SE5 8AF paramala.1.santosh@kcl.ac.uk

Sagar-Ouriaghli I(1), Fiori F(1), Singh J(1)

(1) Department of Child and Adolescent Psychiatry

Introduction: Complex neurodevelopmental disorders require a multi-dimensional treatment plan (Santosh and Singh, 2016, Brit. J. of Psy. Advan. 22: pp. 1-9). Despite this, the clinical effectiveness of treatments is limited in multi-comorbid patients commonly encountered in routine clinical practice. The Centre for Interventional Paediatric Psychopharmacology and Rare Diseases (CIPPRD) is adopting biometric guided therapy to assist in clinical decision-making (Santosh et al., 2016, JCAP, pp. 1-9). Emotional and behavioral dysregulation is common across neurodevelopmental disorders (McLaughlin et al., 2015, J. Am. Acad. Child Adolesc. Psychiatry, 54: pp. 753-762; Dvir et al., 2014, Harv. Rev. Psychiatry, 22: pp. 149-161). Despite this, there is a remarkably paucity in the literature on the impact of the autonomic component on emotional and behavioural regulation in complex neurodevelopment disorders. Unlocking the autonomic component is

crucial to reducing impairment in these disorders. Using wearable sensor technology, we have shown that EBAD (Emotional, Behavioural and Autonomic Dysregulation) is important when treating patients with complex neurodevelopment disorders particularly in those with rare diseases (Santosh et al., 2016, BMC Paediatrics, 16: p. 194; Singh and Santosh, 2016, Psychopharmacology of Neurodevelopmental Disorders in Children pp. 325-362, in Child and Adolescent Psychiatry: Asian Perspective, Springer). Here using wearable sensor technology, we show the symptomatic improvement of patients seen in the CIPPRD treated with the prototypical beta-blocker propranolol. Methods: Children and Adolescents aged 6-19 years who were treated using propranolol as part of their routine care within the CIPPRD were recruited. To explore the autonomic component of EBAD, biometric physiological biomarkers (heart rate [HR] variability and electro-dermal activity [EDA]) were monitored pre- and post-treatment. EDA was analysed using Excel and SPSS software, and as described by Benedek and Kaernbach (2010, J. Neurosci. Methods, 190: pp. 80-91). Heart rate variability analysis software was used to analyse HR variability. Results: Marked variability in HR and EDA was observed in patients pre-treatment; however, these indices of autonomic dysregulation were significantly reduced in patients treated with propranolol, which was reflected by a concomitant shift in the sympathetic and parasympathetic equilibrium. Conclusion: Understanding biometric physiological responses, especially HR variability and EDA (measures of autonomic dysregulation) is important when managing EBAD in patients with complex neurodevelopmental disorders. The use of wearable sensor technology affords clinicians with an effective tool to manage EBAD in these patients and thereby offers a new strategic avenue to improve the care pathway. No sponsorship was received for this study.

C01

FOXO1, A2M AND TGFB1: THREE NOVEL GENES PREDICTING DEPRESSION IN GENE X ENVIRONMENT INTERACTIONS ARE IDENTIFIED USING CROSS-SPECIES AND CROSS-TISSUES TRANSCRIPTOMIC AND MIRNOMIC ANALYSES

Cattaneo A, Psychological Medicine,, Institute of Psychiatry, Psychology & Neuroscience, The Maurice Wohl Clinical Neuroscience Institute, Cutcombe Road, Brixton, London, SE5 9RT annamaria.cattaneo@kcl.ac.uk

Cattane N(1), Czamara D(2), Eriksson J(7), Kajantie E(7), Luoni A(9), Malpighi C(1), Suarez A(4), Lahti J(4), Mondelli V (8), Dazzan P(6), Räikkönen K(4), Binder E(3), Riva MA(9), Pariante CM(5)

(1) Biological Psychiatry Unit, IRCCS Fatebenefratelli S. Giovanni di Dio, Brescia; (2) Department of Translational Research in Psychiatry, Max-Planck Institute of Psychiatry, Munich, Germany; (3) Department of Translational Research in Psychiatry, Max-Planck Institute of Psychiatry, Munich, Germany;; (4) Institute of behavioral sciences, University of Helsinki, Helsinki, Finland; (5) Institute of Psychiatry, Psychology & Neuroscience; (6) Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK;; (7) National Institute for Health and Welfare, Helsinki, Finland; (8) Stress, Psychiatry and Immunology Laboratory, Department of Psychological Medicine, Institute of Psychiatry, King's College, London; (9) University of Milan, Department of Pharmacological and Biomolecular Sciences, Milan, Italy

INTRODUCTION: Depression results from the interplay of vulnerability genes with environmental factors, a phenomenon named as 'gene-environment (GxE) interaction'. To date, GxE interaction studies have been limited to hypothesis-based candidate genes, since genome-wide (GWAS)-based GxE interaction studies would require enormous datasets with genetics, environmental and clinical variables. METHODS: We performed transcriptomic and miRNomic analyses using RatGene 2.1st and miRNA 4.1st Arrays on a GeneAtlas platform (Affymetrix) in the hippocampus of adult rats exposed or not to prenatal stress (PNS); we then integrated these results with transcriptomic data performed with HuGene 2.1st Arrays in blood samples of 40 control subjects characterized for a history of childhood trauma. Statistical and bioinformatics analyses were performed with Partek Genomic Suite and Ingenuity Analyses Software for pathways and network analyses. Selected candidate genes were tested for GXE in two cohorts either with a range of childhood traumatic experiences (Grady Study Project) or with separation from parents in childhood (Helsinki Birth Cohort Study), where GWAS were available. We individually tested SNPs within the selected genes resulting from the final network analysis, calculating both nominal p-values and also multiple testing corrected p-values.

RESULTS: The transcriptomic and miRNOmic analyses identified a significant modulation of 916 genes and of 68 miRNAs in association with PNS (1.2<FC<-1.2, q-value<0.05); a mRNA-miRNAs combining analysis on the same animals allowed the identification of a panel of 528 top-hit genes that were both modulated by PNS exposure and targeted by the miRNAs that were modulated by PNS. These genes were involved in 42 pathways including Axonal Guidance, Protein Kinase-A Signaling, Glucocorticoid Receptor Signaling, TGF-beta Signaling, STAT3 Pathway, ILK Signaling and IL-8 signaling. We then overlapped these 528 genes with the 250 genes that resulted significantly modulated in the blood of subjects in association with childhood trauma, and we found 16 genes as modulated in the same direction. A network analyses on these 16 genes identified only one cluster of interacting genes, which was involved in inflammatory processes and glucocorticoid functionality. These genes were: Forkhead box protein O1 (FOXO1), Alpha-2-Macroglobulin (A2M) and Transforming Growth Factor Beta 1 (TGFB1).

FOXO1, A2M and TGFB1 were then tested for GxE interactions in the two clinical cohorts: six FOXO1 SNPs showed significant GxE interactions with emotional abuse in the Grady Study Project that survived stringent permutation analyses and were all replicated in the Helsinki Birth Cohort Study. In addition, other SNPs in all the three genes showed significant GxE interactions with emotional, physical and sexual abuse in the Grady Study.

CONCLUSION: We therefore provide a successful 'hypothesis-free' approach for the identification and prioritization of candidate genes for GxE interaction studies that can be investigated in GWAS datasets.

FUNDING:This work was supported by the grants "Immunopsychiatry: a consortium to test the opportunity for immunotherapeutics in psychiatry' (MR/L014815/1) and 'Persistent Fatigue Induced by Interferon-alpha: A New Immunological Model for Chronic Fatigue Syndrome' (MR/J002739/1), from the Medical Research Council (UK). Additional support has been offered by the National Institute for Health Research Mental Health Biomedical Research Centre in Mental Health at South London and Maudsley NHS Foundation Trust and King's College London. Dr. Cattaneo is also funded by the Eranet Neuron 'Inflame-D' and by the Ministry of Health (MoH). Professor Raikkonen has received funding from the Finish Academy (No 7631758).

C02

ASSOCIATIONS BETWEEN POLYGENIC RISK SCORES FOR FIVE PSYCHIATRIC ILLNESSES AND BRAIN STRUCTURE USING MULTIVARIATE PATTERN RECOGNITION.

Ranlund S, Neuroimaging, IoPPN, King's College London, Centre for Neuroimaging Sciences, De Crespigny Park, London, UK, SE5 8AF siri.ranlund@kcl.ac.uk

Rosa MJ(2), de Jong S(6), Cole J(1), Fu C(7), Frangou S(5), Mehta MA(3), Dima D(4)

(1) Computational, Cognitive & Clinical Neuroimaging Laboratory, Division of Brain Sciences, Department of Medicine, Imperial College London, UK; (2) Department of Computer Science, University College London, London, UK; (3) Department of Neuroimaging, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK; (4) Department of Neuroimaging, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK and Department of Psychology, School of Arts and Social Sciences, City University London, London, UK; (5) Department of Psychiatry, Icahn School of Medicine at Mount Sinai, USA; (6) NIHR BRC for Mental Health and MRC Social, Genetic & Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London and SLaM NHS Trust, London, UK; (7) School of Psychology, University of East London, London, UK

Introduction: Psychiatric illnesses are complex and polygenic. Some genetic risk factors have been identified, but it remains unclear what effects they have on development of illnesses. The polygenic risk score (PRS) – a measure of the overall genetic risk an individual carries for a disorder – can be used to study functional effects of this genetic risk. Psychiatric illnesses are associated with widespread alterations in grey matter, partly influenced by genetic factors. There have been some attempts to relate PRS to brain structure using univariate methods, mostly within illnesses. However, the PRS captures the combined risk of thousands of variants and is likely associated with widespread effects across the brain. We therefore used multivariate machine learning-based models to investigated associations between brain structure and PRS for five psychiatric disorders; attention deficit-hyperactivity disorder (ADHD), autism, bipolar

disorder, major depression, and schizophrenia. Methods: The sample included 213 individuals from two studies; 69 patients with depression and 70 controls, and 33 patients with bipolar disorder and 41 controls. The five risk scores were calculated based on summary data from the Psychiatric Genomics Consortium. T1-weighted magnetic resonance images were obtained and voxel-based morphometry was implemented in SPM12. Multivariate relevance vector regression was implemented in the Pattern Recognition for Neuroimaging Toolbox; the input features were smoothed, non-modulated, normalised grey matter images, and covariates included age, gender, group status and study. Results: A multivariate pattern of grey matter significantly predicted the PRS for autism (r=0.20, pFDR=0.04; MSE=6.19x10-5, pFDR=0.02). Associations with the schizophrenia PRS reached a trend-level of significance after correction for multiple testing (r=0.15, pFDR=0.08; MSE=1.43x10-5, pFDR=0.02). Associations with PRS for ADHD, bipolar disorder, and depression were not significant. Conclusions: These results lend support to the hypothesis that polygenic liability for autism and schizophrenia is associated with changes in grey matter concentrations, with a widespread pattern of alterations across the brain as anticipated. These associations were seen in individuals not affected by these disorders; they are likely not confounded by illness-specific effects, but associated with a persons' polygenic risk which is normally distributed in the population. The use of PRS has great potential for future research investigating functional effects of genetic risk for psychiatric illnesses. This could include pharmacological studies investigating how drug systems are influenced by an increased genetic risk for a disorder. Part-funding by the National Institute for Health Research Biomedical Research Centre at the South London and Maudsley NHS Foundation Trust and King's College London.

C03

EVIDENCE OF A SEX-SPECIFIC EFFECT OF CALCIUM VOLTAGE-GATED CHANNEL SUBUNIT ALPHA 1 C (CACNA1C) SINGLE NUCLEOTIDE POLYMORPHISMS ON MOOD DISORDER PHENOTYPES WITHIN TWO POPULATION COHORTS

Ferguson A, Public Health, Institute of Health and Wellbeing, 1 Lilybank Gardens University of Glasgow Glasgow, G12 8RZ a.ferguson.3@research.gla.ac.uk

Ward J(3), Graham N(3), Pell J(1), Bailey M(2), Smith DJ(3), Lyall D(1)

(1) As presenting author; (2) Davidson Building, University of Glasgow, G12 8QQ; (3) Gartnavel Royal Hospital,Institute of Health and Wellbeing, 1055 Great Western Road, Glasgow, G12 0XH

Evidence of a sex-specific effect of Calcium Voltage-Gated Channel Subunit Alpha 1 C (CACNA1C) single nucleotide polymorphisms on mood disorder phenotypes within two population cohorts Amy Ferguson, Joey Ward, Nicholas Graham, Jill Pell, Mark Bailey, Donald Lyall, Daniel J. Smith Introduction The Calcium Voltage-Gated Channel Subunit Alpha 1 C (CACNA1C) gene is associated with several neuropsychiatric disorders, including bipolar disorder (BD), schizophrenia and major depressive disorder (MDD) (Cross Disorder Group of Psychiatric Genomics Consortium., 2013, Lancet, 381, 1371–1379). Previous studies investigating pathophysiological correlates of BD-associated CACNA1C SNPs have tended to study single SNPs in isolation, within relatively small samples (Bigos et al., 2010, Arch Gen Psychiatry, 67, 939-945). Methods Our aim was to use a genetic profile risk score (GPRS) approach, combining several BD-associated CACNA1C SNPs, to investigate the association between GPRS and mood disorder-related phenotypes within two large population cohorts (UK Biobank and the Avon Longitudinal Study of Parents and Children; ALSPAC). The phenotypes of interest included hypomania and depressive features (within ALSPAC), and mood instability, neuroticism, BD status and MDD status (within UK Biobank). Only individuals genotyped for all SNPs-of-interest were included for analyses using both ALSPAC (N=7,224) and UK Biobank (N=95,073) Results There were no significant associations between the CACNA1C GPRS and any of the phenotypes investigated in either ALSPAC or UK Biobank. However, previous studies have suggested a potential sex effect of CACNA1C variants (Dao et al., 2010, Biol Psychiatry, 68, 801-810; Heilbronner et al., 2015, European Neuropsychopharmacology, 25, 2262-2270). To investigate this within our samples, the cohorts were divided by sex and the associations were tested in males and females separately. We found weak but significant associations between the CACNA1C GPRS and some of the mood disorder phenotypes in females. Within ALSPAC, in unadjusted regressions, an increased GPRS was associated with decreased hypomania score (P=0.05) and increased depression score (P=0.03) in females (N=1,326). In UK Biobank, a significant association between increased CACNA1C GPRS score and BD status (P=0.03) was identified

in females (N=12,454) even after adjustment for confounders. Conclusion Overall, these associations provide further evidence of a potential sex effect of CACNA1C variants. Calcium channel antagonists have previously been reported to have some efficacy in bipolar disorder (Keers et al., 2009, Psychological Medicine,39, 1231-1235); our findings might suggest that they may have greater efficacy in female BD patients rather than males. This project is financially supported by a Medical Research Council Doctoral Training Programme Studentship to AF.

C04

GENOME-WIDE ANALYSIS OF 113,968 INDIVIDUALS IN UK BIOBANK IDENTIFIES FOUR LOCI ASSOCIATED WITH MOOD INSTABILITY

Ward J, Health & Wellbeing, University of Glasgow, Research Assistant Mental Health and Wellbeing Gartnavel Royal Hospital Admin building, 1st Floor 1055 Great Western Road Glasgow, G12 OXH joey.ward@gla.ac.uk

Strawbridge R(1), Graham N(1), Bailey M(1), Ferguson A(1), Lyall D(1), Cullen B(1), Pidgeon L(1), Cavanagh J(1), Mackay D(1), Pell J(1), O'Donovan M(1), Escott-Price V(1), Smith D(1)

(1) Health & Wellbeing

Mood instability is a core clinical feature of affective disorders, particularly major depressive disorder (MDD) and bipolar disorder (BD). It may be a useful construct in line with the Research Domain Criteria (RDoC) approach, which proposes studying dimensional psychopathological traits that cut across diagnostic categories as a more effective strategy for identifying the underlying biology of psychiatric disorders. Here we report a genome-wide association study (GWAS) of mood instability in a very large study of 53,525 cases and 60,443 controls from the UK Biobank cohort, the only such GWAS reported to date. We identified four independent loci (on chromosomes eight, nine, 14 and 18) significantly associated with mood instability, with a common SNP-based heritability estimate for mood instability of approximately 8%. We also found a strong genetic correlation between mood instability and MDD (0.60, SE=0.07, p=8.95x10-17), a small but statistically significant genetic correlation with schizophrenia (0.11, SE=0.04, p=0.01), but no genetic correlation with BD. Several candidate genes harbouring variants in linkage disequilibrium with the associated loci may have a role in the pathophysiology of mood disorders, including the DCC netrin 1 receptor (DCC), eukaryotic initiation factor 2B (EIF2B2), placental growth factor (PGF) and protein tyrosine phosphatase, receptor type D (PTPRD) genes. Strengths of this study include the large sample size; however, our measure of mood instability may be limited by the use of a single self-reported question. Overall, this work suggests a polygenic basis for mood instability and opens up the field for the further biological investigation of this important cross-diagnostic psychopathological trait. Funding comes from the Royal College of Physicians of Edinburgh.

C05

A META-ANALYSIS OF REWARD PROCESSING DIFFERENCES BETWEEN DEPRESSED AND HEALTHY INDIVIDUALS

Halahakoon DC, Institute of Cognitive Neuroscience, UCL, Fourth Floor, Alexandra House, 17-19 Queen Square, London, WC1N 3AR c.halahakoon@ucl.ac.uk

Roiser JP(1)

(1) As presenting author

Introduction Concepts such as reward processing (RP) may provide a valuable framework for understanding the latent factors underlying depressive symptoms (Eshel N, Roiser JP, 2010, Biological Psychiatry. 68:118-124). Several studies have reported RP differences between healthy volunteers (HV) and individuals with major depressive disorder (MDD). Other studies report no such differences. The purpose of this meta-analysis was to assess whether there is evidence in the literature for differences in RP between MDD and HV. Methods A literature search was carried out in December 2015 on the Medline and Psychinfo databases. Of 1421 search results, 21 case-control studies of depressed individuals and healthy controls using RP tasks with explicit rewards (money, points or basic reinforcers) were included in the

meta-analysis. Standardized mean differences (Cohen's d) for group differences in performance on the RP tasks were calculated for each paper and synthesized using standard meta-analytic techniques. Since "reward processing" is unlikely to represent a unitary construct, several sub-categories of RP were also defined according to the specific cognitive process assessed in the task: value; value-based choice; effort; and learning. Results The total sample size was 1133 (MDD: 604, HV: 529). The average weighted effect size (ES) for RP differences between the two groups was 0.314 (95%CI: 0.133-0.495). Accounting for publication bias (using trim and fill), the overall ES was reduced to 0.279 (95%CI: 0.093-0.466). When the 9 studies that included only unmedicated MDD in the case group were analysed (total sample size 481, MDD: 249, HV: 232), the average weighted ES was 0.379 (95%CI: 0.080-0.677) with no change when publication bias was accounted for. The ESs for individual components of RP were: value (ES 0.467, 95% CI: 0.29-0.906); value-based choice (ES 0.409, 95% CI: 0.204-0.614); effort (ES -0.087, 95% CI: -0.425-0.251); learning (ES 0.569, 95% CI: 0.2-0.938). Conclusions The results of this meta-analysis suggest that there exist small-to-medium differences in RP between depressed and healthy populations. The relatively small size of this effect may, in part, reflect inter-study heterogeneity (populations and behavioural-paradigms) and the biological heterogeneity inherent in using symptom-clusters as categorisation criteria (i.e. HC vs MDD). Bar effort, all explored subcomponents of RP appear to be significantly affected in depression. If concepts such as RP prove to be sufficiently robust, they may allow for a more biologically based nosology of psychiatric conditions and facilitate advances in the development of investigations and treatments. DCH and JPR are funded by the Wellcome Trust.

C06

ATYPICAL DEPRESSION AND NON-ATYPICAL DEPRESSION: IS HPA AXIS FUNCTION A BIOMARKER? A SYSTEMATIC REVIEW

Juruena MF, Centre for Affective Disorders, Psych Med, IoPPN, Room E2.08 PO72, De Crespigny Park Denmark Hill, London, SE5 8AF mario.juruena@kcl.ac.uk

Bocharova M(1), Agustini B(1), Young AH(1)

(1) Centre for Affective Disorders, Psych Med-IoPPN, KCL

The link between the abnormalities of the Hypothalamic-pituitary-adrenal (HPA) axis and depression has been one of the most consistent findings in psychiatry. At the same time, while multiple studies have demonstrated a stronger association between the increased activation of HPA-axis and melancholic, or endogenous, depression subtype, the atypical subtype has been associated with a decrease in HPA-axis function. The precise association between the direction of the HPA-axis-related disturbances and depression subtype has not been established yet. The purpose of this systematic review is to summarise existing studies addressing the abnormalities of the HPA-axis in melancholic and/or atypical depression. We conducted a systematic search in the literature by searching MEDLINE, PsycINFO and Embase databases. The following search items were used: "hypothalamic-pituitary-adrenal" OR "HPA" OR "cortisol" OR "corticotropin releasing hormone" OR "corticotropin releasing factor" OR "glucocorticoid*" OR "adrenocorticotropic hormone" OR "ACTH" AND "atypical depression" OR "non-atypical depression" OR "melancholic depression" OR "non-melancholic depression" OR "endogenous depression" OR "non-endogenous depressive. All studies were scrutinised to determine the main methodological characteristics, and particularly possible sources of bias influencing the results, using the STROBE statement checklist. We selected 56 studies. Detailed analysis of the methodologies used in the studies revealed significant variability especially regarding the samples' definition comparing the HPA axis activity of melancholic to atypical depression, including healthy controls. The results were subdivided into 3 sections: 1) including 35 studies which compared «melancholic» OR «endogenous» depression vs. «non-melancholic» or «non-endogenous» depression; 2) including 14 studies which compared «atypical depression» or atypical traits vs. «non-atypical» depression; and 3) including 7 studies which examined «melancholic» or «endogenous» and «atypical» depression subtypes. While the majority of studies did confirm the association between melancholic depression and either increased basal or increased post-challenge cortisol levels, more robust associations were demonstrated for particular vegetative symptoms. At the same time, most patients suffering from atypical depression showed either decreased levels of HPA-axis activity or comparable with those as healthy control, with stronger associations demonstrated for «reversed vegetative symptoms»,

such as hypersomnia or increased appetite/weight gain. Whether «mood reactivity», other criteria for atypical depression is associated with particular biomarkers, remains unclear. This systematic review confirms that there is a general evidence that there are differences in HPA-axis function between melancholic and atypical depression, although a more precise evaluation of the dichotomy would require focusing on biological symptom clusters and endophenotype rather than syndromes subtypes. Financial support from Academy Medical Sciences.

C07

EARLY ONSET OF LITHIUM RELAPSE PREVENTION IN BIPOLAR DISORDER

Taylor MJ, Psychosis Studies, IOPPN, King's College London, SE5 8AF matthew.j.taylor@kcl.ac.uk

Introduction Understanding the timing of action of the clinical effects of treatments is not only of clinical relevance, but also provides key information to guide investigations of their underlying mechanisms. Lithium remains the prototypical mood stabiliser. It has well-established clinical benefits in the treatment of bipolar disorder, but its mechanisms of action have remained an area of debate. This has complicated efforts to develop lithium mimetic treatments. We sought to clarify the timing of onset of action of lithium in relapse prevention for bipolar disorder using data from large scale clinical trials. Methods Data were extracted from three placebo-controlled randomised trials of lithium in the prevention of relapse in bipolar I disorder that presented suitable survival curve data for analysis. Pooled estimates of interval hazard ratios (HR) were obtained using a random effects model using meta in R. Results An early reduction in risk of recurrent mood episodes was apparent in those randomised to lithium compared to those randomised to placebo. The effect was apparent over the period from randomisation to week 3, HR 0.58 (95% CI 0.40 to 0.84). For manic relapse alone a similar effect was seen, HR 0.41 (95% CI 0.24 to 0.73) from randomisation to week 4. However, an early effect on depressive relapse was not clearly shown, HR 0.84 (95% CI 0.51 to 1.38) over the same period. Conclusions There is evidence from existing clinical trials for an early onset of action of lithium in relapse prevention in bipolar disorder. Available data suggest this early effect may be driven by reduction in risk of manic relapse rather than depressive relapse. The effects seen are of similar magnitude to those reported in previous conventional meta-analyses assessing total relapses over longer periods of follow-up. These early clinical effects may have implications for the design of studies investigating lithium mechanisms of action. No sponsorship was received for this study.

C08

SERUM FACTORS AS PREDICTORS OF INTERFERON-ALPHA (IFN-A)-INDUCED DEPRESSION

Borsini A, Psychological Medicine, King's College London, Institute of Psychiatry, Psychology and Neuroscience, The Maurice Wohl Clinical Neuroscience Institute Cutcombe Road London, UK, SE5 9RT alessandra.borsini@kcl.ac.uk

Hepgul N(3), Russell A(1), Zajkowska Z(1), Zunszain PA(1), Pariante CM(1), Thuret S(2)

(1) As presenting author; (2) Centre for the Cellular Basis of Behaviour, King's College London, Institute of Psychiatry, Psychology and Neuroscience; (3) UK Health Services and Population Research, King's College London, Institute of Psychiatry, Psychology and Neuroscience

IFN-alpha is the standard treatment for chronic hepatitis C virus (HCV) infection, which causes high rates of depression (Asnis, G.M., et al., 2006, Journal of Clinical Gastroenterology 40,322-335). However, the biological factors that predispose an individual to the occurrence of depression are still unknown. Previous data have reported an alteration in the serum level of inflammatory markers in depressed, when compared with non-depressed patients. There is in fact evidence for serum factors to penetrate the blood brain barrier and modulate different brain signalling (Villeda, S.A., et al., 2011, Nature 477,90-94). This study investigates whether co-incubation of human hippocampal progenitor cells (HPCs) with serum from IFN-alpha treated HCV patients differently affect human hippocampal progenitor cell fate, when comparing serum from patients who will and will not later develop depression. Serum samples were collected at baseline, before the IFN-alpha treatment begins (treatment week (TW) 0) and at TW4 from 33 HCV patients; 9 of these patients later developed IFN-alpha induced depression. The multipotent human hippocampal progenitor cell line HPC03A/07 was used to evaluate the effects of serum. Cells were co-incubated with serum samples under

proliferating conditions for 2 days, followed by differentiating conditions for 7 days. During proliferation, apoptotic cells were evaluated by immunostaining with caspase 3 (CC3), whereas neuronal differentiation was assessed with doublecortin (DCX). Treatment with TW0 serum from depressed patients increased the percentage of CC3+cells ($U=49.5$, $p<0.05$), when compared with serum from non-depressed. However, there was no difference in the percentage of DCX+cells ($U=81$, $p=0.3$) between the two groups. In contrast, treatment with TW4 serum from non-depressed patients increased the percentage of DCX+cells ($U=56$, $p<0.05$), when compared with depressed. However, there was no significant difference in the percentage of CC3+cells ($U=100$, $p=0.8$) between the two groups. Indeed, the increase in the percentage of DCX+cells was significantly higher upon treatment with serum samples from non-depressed than from depressed patients, when comparing TW4 with TW0 ($F(1,31)=5.3$; $p<0.05$). No significant difference was reported in the percentage of CC3+cells between depressed and non-depressed patients, when comparing TW4 with TW0 ($F(1,31)=0.8$; $p=0.4$). Our findings show that blood factors contained in serum of HCV patients who will later develop depression modulate both the process of apoptosis and neuronal differentiation. Future analyses should allow for the detection of serum factors involved in the alteration of cell death and neurogenesis, which may contribute to the advancement of novel therapeutic strategies for the prevention of IFN-alpha induced depression. This work was supported by the Janssen Pharmaceutical NV/Janssen Pharmaceutical Companies of Jonhson&Jonhson, 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.

C09

THE ROLE OF ENDOCANNABINOIDS IN INFLAMMATION-INDUCED DEPRESSION

Zajkowska Z, Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, The Maurice Wohl Clinical Neuroscience Institute Cutcombe Road London, SE5 9RT zuzanna.zajkowska@kcl.ac.uk

Russell A(4), Hepgul N(1), Borsini A(4), Forton D(2), Agarwal K(3), Zunszain PA(4), Mondelli V(4), Pariante CM(4)

(1) Cicely Saunders Institute, Department of Palliative Care, Policy and Rehabilitation Bessemer Road, Denmark Hill, London, SE5 9PJ; (2) Department of Gastroenterology & Hepatology, St George's University of London, Blackshaw Rd, London, SW17 0QT; (3) Institute of Liver Studies, King's College Hospital, London, SE5 9RS; (4) The Maurice Wohl Clinical Neuroscience Institute, Cutcombe Road, London, SE5 9RT

A reduced activity of the endocannabinoid (eCB) system is implicated in depression (Hill et al., 2008, Pharmacopsychiatry, 41: 48 – 53). The eCB system also participates in the immune system regulation. As such, immune stimulation have been shown to increase the eCB activity (Berdyshev et al., 2001, The FASEB Journal, 15: 2171-2178). Interestingly, there is a well-established link between immune activation and depression, such as following the administration of the pro-inflammatory cytokine, interferon-alpha (IFN-α), used to treat hepatitis C viral (HCV) infection (Raison et al., 2005, J Clin Psychiatry, 66(1): 41-48). However, the role of the eCB system in the inflammation-induced depression has never been explored. In this study, we investigated whether circulating eCBs are involved in the mechanisms underlying depression development in patients receiving IFN-α treatment for HCV infection. We measured serum concentrations of anandamide (AEA) and 2-arachidonoylglycerol (2-AG) in 70 patients and 55 healthy controls, at baseline, treatment weeks 4 and 24, and six months follow up (6mFU), using High Performance Liquid Chromatography with Tandem Mass Spectrometry. We used M.I.N.I. International Neuropsychiatric Interview to assess depression development. Patients were divided according to whether they developed depression, or not, during IFN-α treatment. Our results show that HCV patients had lower AEA levels (0.93 ± 0.05) compared with controls (1.18 ± 0.05) at baseline ($t = -4.040$, $p<.001$), whereas there was no difference in 2-AG levels (HCV: 6.28 ± 0.55; controls: 5.88 ± 0.81; $p = .22$). There was no baseline difference between patients who did, and did not develop depression during treatment, in AEA (depressed: 0.93 ± 0.06, not depressed: 0.93 ± 0.08; $t = .264$, $p = .79$) and 2-AG levels (depressed: 5.22 ± 0.66, not depressed: 6.99 ± 0.78; $U = 600.000$, $z = -1.337$, $p = .18$). Interestingly, AEA and 2-AG concentrations significantly increased during treatment in the whole sample (AEA: $F = 73.657$, $p<.001$; 2-AG: $F = 47.899$, $p<.001$). However, there were

no differences in AEA and 2-AG levels between depressed and non-depressed patients during treatment (AEA: F = .211, p = .81; 2-AG: F = 1.302, p = .28). 2-AG levels normalized at 6mFU (baseline: 6.38±0.81, 6mFU: 6.39±0.58; t = -.003, p = .99), whereas AEA levels remained elevated in the whole sample (baseline: 0.91±0.05, 6mFU: 1.46±0.08; t = -7.635, p<.001). The increase in AEA and 2-AG following IFN-α treatment suggests the involvement of the eCB system in immunomodulation, but whether or not this influences the development of depression, is not adequately captured by the measurement of serum AEA and 2-AG. This study represents independent work supported by the Medical Research Council (UK) MR/J002739/1 and the Commission of European Communities Seventh Framework Programme (Collaborative Project Grant Agreement no. 22963, Mood Inflame), and part funded by the NIHR/Wellcome Trust, King's Clinical Research Facility and the National Institute for Health Research (NIHR) Biomedical Research Centre [and Dementia Unit] at South London and Maudsley NHS Foundation Trust and King's College London.

C10

THE ROLE OF CARDIOVASCULAR ASSOCIATED INFLAMMATORY MARKERS IN DEVELOPMENT OF DEPRESSION

Nikkheslat N, Psychological Medicine, Psychiatry, Psychology & Neuroscience, Kings College London, Stress, Psychiatry and Immunology Laboratory, Room G.30.2, The Maurice Wohl Clinical Neuroscience Institute, Cutcombe Road, Brixton, London, SE5 9RT naghmeh.nikkheslat@kcl.ac.uk

Zunszain PA(3), Tylee A(2), Carvalho LA(1), Pariante CM(3)

(1) William Harvey Research Institute,Queen Mary University of London Charterhouse Square, London, EC1M 6BQ; (2) Health Service and Population Research Dept, Inst of Psychiatry, KCL, London; (3) Inst of Psychiatry, Psychology & Neuroscience,The Maurice Wohl Clinical Neuroscience Institute, Cutcombe Road, London SE5 9RT

Introduction: Depression is a debilitating condition and although there are effective antidepressants available, one third of depressed patients do not respond to conventional treatments (Ferrari et al., 2013, PLoS Med, 10, e1001547). Depression is highly prevalent in heart disease patients increasing the risk of adverse cardiac outcome. However, the physiological mechanisms underlying the increased incidence of depression in patients with heart disease are yet to be understood. Inflammation is recognised as a common link between these two disorders (Halaris, 2013, Curr Psychiatry Rep, 15: 400). The present study aimed to evaluate the role of inflammation in development of depression in coronary heart disease (CHD) patients by investigating the two major cardiovascular related inflammatory markers, C-reactive protein (CRP) and vascular endothelial growth factor (VEGF), as predicting biomarkers for future development of depression. Methods: We included ninety-one CHD patients (male 78%, mean ± SD age 68.29 ± 1.87 years) from primary care services in South London (Ethics REC REF 09/H1103/19). Participants were assessed for depressive symptoms by means of patient health questionnaire-9 (PHQ-9) at baseline and then followed up every six months for 3 years. Biological assessments were obtained at baseline including serum CRP and plasma VEGF that were measured using commercially available ELISA kits. Correlation, and multiple linear and logistic regression analysis were performed to investigate associations between elevated inflammatory markers with severity of symptoms and subsequent development of depression. Results: Our results show that higher CRP levels were associated with severity of depression at baseline (r=0.218, p=0.038). Increased VEGF concentrations also showed a trend towards increased severity of depressive symptoms (rs=0.268, p=0.069). In CHD patients without depression (51.6%), higher CRP risk factor at baseline was associated with development of depression after 3 years (=0.990, p=0.024). Joint elevation in the levels of peripheral CRP and VEGF in CHD non-depressed at baseline predicted greater depressive symptoms at follow up but only reached a statistical trend (F=2.716, p=0.083). Conclusions: Activated inflammatory response in heart disease patients is associated with future development of depression. Inflammation may be considered as a target for prevention or treatment of depression in inflammatory associated disorders. Better understanding of the biological mechanisms involved in pathophysiology of depression would lead to development of more successful and personalized therapeutic strategies. This study was supported by the NIHR BRC, BHF, EU-FP7, ECNP and NARSAD Young Investigator Awards.

C11

INVESTIGATING THE LINK BETWEEN CHILDHOOD TRAUMA, CORTISOL LEVELS, INFLAMMATION, AND RESPONSE TO TREATMENT IN PATIENTS WITH DEPRESSION

McLaughlin AM, Psychological Medicine, King's College London, Cutcombe Road, Brixton, London, SE5 9RT anna.mclaughlin@kcl.ac.uk

Nikkhleshat N(5), Hastings C(5), Nettis MA(5), Zajowska Z(5), Mariani N(5), Wellcome Trust Neuroinflammation Consortium BIODEP(1), Cowen C(6), Cavanagh C(4), Harrison N(2), Bullmore E(3), Pariante CM(5), Mondelli V(5)

(1) Cambridgeshire & Peterborough National Health Service (NHS) Foundation Trust & University of Cambridge, UK; (2) Department of Neuroscience, Brighton & Sussex Medical School, University of Sussex, Brighton, UK; (3) Department of Psychiatry, Behavioural and Clinical Neurosciences Institute, University of Cambridge, UK; (4) Mental Health and Wellbeing, Sackler Institute, Neurology block, Queen Elizabeth University Hospital, Glasgow, UK; (5) Stress, Psychiatry & Immunology Laboratory at the Institute of Psychiatry, Psychology & Neuroscience, Kings College London, UK; (6) University Department of Psychiatry, Warneford Hospital, Oxford, UK

Introduction: Childhood trauma has been associated with increased risk of depression and poorer response to antidepressants (Williams LM, et al., 2016, Translational Psychiatry, 6:e799). Childhood trauma has also been associated with increased inflammation and hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis in adulthood (Lu S, et al., 2016, Journal of Psychiatric Research 78: 24–30), and although patients with depression often present with HPA axis hyperactivity and increased inflammation, it remains unclear to what extent childhood trauma may contribute to these. We investigated whether childhood trauma predicts increased cortisol levels, increased inflammation and antidepressant response, in three clinically characterised subgroups of patients with depression and healthy controls. Methods: Clinical data, blood and saliva samples have been collected in 158 patients with depression (38 remitted patients, 81 medicated patients and 39 unmedicated patients) and 46 healthy controls, as part a multicenter study investigating immune biomarkers in depression (BIODEP). Preliminary analyses have been completed on 14 unmedicated patients with depression (mean age: 35.1 years, 50% female) and 10 controls (mean age: 35.4 years, 50% female). Childhood trauma data was collected using the Childhood Trauma Questionnaire (CTQ). High sensitive C reactive protein (CRP) was measured from serum samples. Saliva samples were collected at multiple time points to measure Cortisol Awakening Response (CAR) and diurnal cortisol levels. Results: Unmedicated patients and controls did not significantly differ in CAR (mean±SEM: 588.7±97.4 vs. 842.4±135.9 nmol min/l, p=0.1) and diurnal cortisol levels (58.9±38.4 vs 62.3±9.0 nmol h/l, p=0.8). Within the patient group, CAR was correlated with total CTQ score (r=0.66, p=0.01), and diurnal cortisol levels and total CTQ scores were correlated at trend-level (r=0.45, p=0.1); these correlations were not observed in controls (r=0.24, p=0.95 and r=0.26, p=0.47 respectively). After excluding subjects with CRP levels above 10mg/dl, we found a positive correlation between CRP levels and CTQ sexual abuse score within the patient group (r=0.65, p=0.03). There was a trend for a correlation between CAR and CRP (r=0.58, p=0.08) within the patient group, but not in the control group (p=0.8). Conclusion: Our preliminary analyses suggest history of childhood trauma is associated with increased cortisol levels and increased CRP, in unmedicated depressed patients. This will be the first study large enough to investigate whether these variables differ according to depression severity, remission and antidepressant use, providing valuable insight into the pathophysiology of depression and appropriate pharmacological intervention. Acknowledgments: BIODEP is funded by the Wellcome Trust, Janssen, Lundbeck, Pfizer and GlaxoSmithKline.

C12

EXPRESSION CHANGES OF INFLAMMATION-RELATED GENES IN THE BLOOD MRNA OF PATIENTS WITH DEPRESSION: A STUDY IN TREATMENT RESISTANT, TREATMENT RESPONSIVE, OR UNTREATED PATIENTS

Mariani N, Psychological Medicine, Institute of Psychiatry, Psychology & Neuroscience, Kings College London The Maurice Wohl Clinical Neuroscience Institute Cutcombe Road, London SE5 9RT, SE5 9RT nicole.mariani@kcl.ac.uk

Cattaneo A(5), Malpighi C(3), McLaughlin AP(5), Nikkhleshat N(5), Hastings C(5), Nettis MA(5), Zajowska Z(5), Byrom H(5), Cowen P(7), Cavanagh J(6), Harrison N(4), Bullmore E(2), The Wellcome Trust Neuroimmunology of Mood Disorders and Alzheimer's Disease (1), Mondelli V(5), Pariante CM(5),

(1) (NIMA) Consortium; (2) Behavioral and Clinical Neuroscience Institute and Department of Psychology, University of Cambridge, Cambridge, UK; (3) Biological Psychiatry Unit, IRCCS Fatebenefratelli San Giovanni di Dio, Brescia, Italy; (4) Brighton and Sussex Medical School, University of Sussex Campus, Brighton, UK; (5) Department of Psychological Medicine, King's College London, Institute of Psychiatry, Psychology and Neuroscience; (6) Mental Health and Wellbeing, Sackler Institute, Neurology block, Queen Elizabeth University hospital, Glasgow, UK; (7) University Department of Psychiatry, Warneford Hospital, Oxford, UK

Introduction: Depressed patients have high levels of inflammation, but whether this is influenced by current antidepressant treatment is currently unclear, especially if patients are not responding to the antidepressant. We have previously shown that high levels of IL-1b and Macrophage Inhibiting Factor (MIF) gene expression from blood mRNA characterize a subgroup of depressed patients who are resistant to conventional antidepressants (Cattaneo et al., Neuropsychopharmacology. 2013;38(3):377-85; Cattaneo et al., Int J Neuropsychopharmacol. 2016,19(10)). Here we aim to investigate a broader range of inflammatory genes in three well-characterised group of depressed patients who were treatment resistant, treatment responsive, or untreated, and in controls. Methods: Clinical data and blood mRNA from Paxgene tubes have been collected in 188 patients with depression (including 48 untreated, 92 treatment resistant, and 48 treatment responsive) and in 52 healthy controls, as part of BIODEP, a multicenter study investigating immune biomarkers in depression within the NIMA Consortium. We have completed analysis on a preliminary sample of 18 untreated patients, 24 treatment resistant patients, 22 treatment responsive patients, and 10 controls. Mean age of all groups were ranging 35-36 years, 50% female. Using qPCR, we have measured IL-1b, TNF-alpha, MIF, and Alpha-2-Macroglobulin (A2M). Results: Compared with controls, all three groups of depressed patients had higher levels of IL-1b (ranging +11-24%, $p<0.05$), TNF-alpha (ranging +12-18%, $p<0.05$) and MIF (ranging +20-28%, $p<0.05$); only untreated and treatment resistant patients had higher levels of A2M (+15% and 18%, $p<0.05$). Conclusion: Our preliminary analyses confirm that increased IL1b and MIF gene expression is a consistent marker of inflammation in depressed patients. Once all the samples will be analysed, this will be the largest study with well clinically-characterised depressed-patents and concomitant measurements of immune genes and proteins. Acknowledgments: The Neuroimmunology of Mood Disorders and Alzheimer's Disease (NIMA) consortium is funded by the Wellcome Trust, Janssen, Lundbeck, Pfizer and GlaxoSmithKline.

C13

THE ROLE OF CORTISOL LEVELS IN THE RESPONSE TO ANTIGLUCOCORTICOID TREATMENT IN PATIENTS WITH MOOD DISORDERS: A SYSTEMATIC REVIEW

Lombardo G, Psychological Medicine King's College London, Institute of Psychiatry, Psychology and Neuroscience King's College London, Maurice Wohl Clinical Neuroscience Institute 5 Cutcombe Rd, Brixton, London SE5 9RT London, SE5 9RT giulia.lombardo@kcl.ac.uk

Gianotti L(1), Pariante CM(2), Mondelli V(2)

(1) Endocrinology Diabetology and Metabolism - AO s. Croce e Carle Cuneo, via Michele Coppino, 26, 12100 Cuneo CN, Italy; (2) Institute of Psychiatry, Psychology and Neuroscience King's College London, Department of Psychological Medicine - Maurice Wohl Clinical Neuroscience Institute, G.33.76 Cutcombe Road London SE5 9RT

A large body of literature has previously shown the presence of a hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis in patients with mood disorders, as reflected by high levels of cortisol in these patients. The HPA axis has therefore been considered as a potential target for pharmacological therapy for depression. In particular, several clinical trials have tested the efficacy of antiglucocorticoid medications in this population. However, as previously discussed by Gallagher (Gallagher et al., 2009. Cochrane Database of Systematic Reviews, Issue 1 "Antiglucocorticoid treatments for mood disorders"), clinical trials have generated inconsistent results regarding the efficacy of antiglucocorticoid treatment in improving depressive symptoms or neurocognitive function. One of the possible reasons behind this inconsistency may lie on the evidence that not all patients with mood disorders show a hyperactivity of HPA axis; it is possible to hypothesize that the different baseline cortisol levels can influence the response to antiglucocorticoid treatment. The aim of this systematic review is to investigate whether baseline cortisol levels or changes in cortisol levels during antiglucocorticoid treatment can moderate the efficacy of antiglucocorticoid drugs in patients with mood disorders. We systematically reviewed the literature from inception until February 2017 to identify studies which have investigated efficacy of antiglucocorticoid drugs in patients with mood disorders and measured cortisol levels. We selected only papers published in English and studies conducted in patients suffering with Major Depression Disorder (MDD), Psychotic Major Depression (PMD), Bipolar Disorder (BD). The keywords used in search engine PubMed, Science Direct, Scopus were: "Depression", "Mood Disorders", "Antiglucocorticoid", "Treatment-Resistant Depressed (TRD)", "Glucocorticoid Antagonist", "Cortisol", "Cortisol antagonist", "Hypothalamic-pituitary-adrenal", "Ketoconazole", "Mifepristone", "Metyrapone". We have so far identified 15 papers investigating the efficacy of antiglucocorticoid treatment in patients with mood disorders and analysed cortisol levels in the same patients. Thirteen studies investigated depressive symptoms, two studies focussed on neurocognitive function. From the 15 papers, seven studies observed an association, between changes in cortisol levels and clinical outcome (i.e. depressive symptoms or cognitive function) . On the other hand, six did not find an association between cortisol levels at the baseline, or changes in cortisol levels during the treatment, and an improvement in depressive symptoms. Two articles did not detect changes in cortisol levels The preliminary results of the review suggest that antiglucocorticoid treatment may improve depressive symptoms and neurocognitive function in patients with mood disorders mainly when associated with changes in HPA axis activity. Aknowledgment: No financial sponsorship.

C14

EFFECTS OF SSRIS ON INFLAMMATORY MARKERS IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER: A SYSTEMATIC REVIEW AND META-ANALYSIS

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

Wang L(2), Wang R(2), Qiao D(2), Baldwin DS(1)

(1) Department of Psychiatry, University of Southampton, 4-12 Terminus Terrace, Southampton, SO143DT; (2) Shandong Mental Health Centre, Jinan Shandong, China, 250014

Introduction: Peripheral levels of inflammatory markers are elevated in major depressive disorder (MDD). Selective serotonin reuptake inhibitors (SSRIs) affect levels of inflammatory markers in patients with MDD, but studies have reported inconsistent findings. This systematic review and meta-analysis aims to investigate the effects of SSRIs treatment on peripheral levels of a range of inflammatory markers in MDD patients. Methods: Systematic literature search (Pubmed, Web of Science, Embase, Cochrane) for trials published before November 2016 were conducted. Studies were included if they used SSRI monotherapy and peripheral levels of interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-10, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ were measured before and after treatment in patients with MDD. Meta-analysis was conducted using Comprehensive Meta-analysis (version 2). Effect sizes were calculated using bias-corrected standardized mean difference (Hedges' g) between pre- and post-treatment. Sub-group analyses and publication bias estimates were undertaken; sensitivity analyses were performed using different estimated pre- and post-treatment correlations and after removing poor quality studies. Results: Sixteen eligible studies including 570 MDD patients were included in the meta-analysis: 10 studies for IL-6; 7 for TNF-α; 5 for IL-1β, IL-4 and IL-10; 4 for IL-2; and 3 for IFN-γ. The pooled effect estimate indicates SSRI

treatment decreased levels of pro-inflammatory markers IL-6 (Hedges' g, -0.428; 95%CI, -0.699 to -0.158; I2=84.867) and IL-1β (Hedges' g=-0.873; 95%CI, -1.702 to -0.043; I2=94.237), and anti-inflammatory marker IL-10 (Hedges' g=-0.535; 95%CI, -0.987 to -0.084; I2=84.369). There were no significant treatment effects on levels of IL-2, IL-4, TNF-α, or IFN-γ. There was a high level of heterogeneity between studies. Sub-group analyses on studies involving IL-6 indicated the high heterogeneity was not explained by age, gender, sample size, drug dosage, study duration or study design. No evidence of publication bias was found. Sensitivity analyses indicated the robustness of the primary analyses. Conclusions: High heterogeneity between studies limits interpretation, but meta-analysis indicates moderate immunoregulatory effects of SSRIs treatment for MDD, which suggests SSRIs may owe some of their therapeutic effect to their anti-inflammatory properties. Funding: This work was funded by an exchange award from the People's Republic of China State Administration of Foreign Experts Affairs to Shandong Mental Health Centre and University of southampton (2016/17: P152023038).

C15

A SYSTEMATIC REVIEW OF ANTI-INFLAMMATORY AGENTS IN THE TREATMENT OF MOOD DISORDERS

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

Cheng X(2), Li R(2), Yang Y(2), Liu J(2), Zhang J(2), Baldwin DS(1)

(1) Dept of Psychiatry, Univ of Southampton, 4-12 Terminus Terrace, Southampton SO14 3DT; (2) Shandong Mental Health Centre, Jinan Shandong, China 250014

Introduction: Inflammatory processes have been implicated in the pathophysiology and progression of mood disorders, and anti-inflammatory drugs have been used to enhance antidepressant treatment response. This systematic review evaluates current knowledge of the effects of anti-inflammatory agents as adjunctive treatment or in monotherapy for patients with mood disorders. Methods: Literature search (using PubMed and Embase) of randomised controlled trials (RCTs) which investigated the effects of anti-inflammatory drugs in mood disorders, published before October 2016, supplemented by manual searches. Screening, data extraction and quality assessment were conducted. The primary outcome measures were measures of depression and manic symptoms. A sub-analysis was performed based on adjunctive treatment or monotherapy. Results: Thirty-six completed RCTs (including 1775 participants) with treatment duration varying from 4 to 28 weeks met study inclusion criteria, were identified and included in this review, including studies of omega-3 fatty acids (n=15), N-acetylcysteine (n=7), non-steroidal anti-inflammatory drugs (n=6), pioglitazone (n=3), statins (n=3), a tumor necrosis factor antagonist (n=1), and antibiotics (n=1). 4 RCTs investigated monotherapy with omega-3 fatty acids, and 32 studies investigated adjunctive anti-inflammatory agents. At the endpoint of the study period, 20 of the 32 RCTs adjunctive use of anti-inflammatory drugs pronounced a significant improvement in depressive symptoms ($P < 0.05$), including 16 RCTs assessed by Hamilton Depression Rating Scale (HDRS) with a score variation range from -3.6 to -19.0 (treatment groups) vs -1.9 to -15.8 (placebo groups); 3 studies evaluated by Montgomery-Asberg Depression Rating Scale (MADRS) with a score decrease range from -10.0 to -18.2 (treatment groups) vs +0.9 to -8.8 (placebo groups); and 1 RCT adopting Geriatric Depression Scale (GDS) as the primary outcome measure with a score reduction of -4.5 (treatment group) vs -0.8 (placebo group). With respect to manic symptoms, 4 of the 11 studies on adjunctive anti-inflammatory agents demonstrated a notable amelioration in bipolar disorder ($P < 0.05$), with the reduction of Young Mania Rating Scale (YMRS) score varied from -2.0 to -29.8 (treatment groups) vs 0 to -21.8 (placebo groups). Only 1 of the 4 studies estimating monotherapy of omega-3 fatty acids showed a significant antidepressant benefit ($P < 0.05$). Conclusions: Data from eligible RCTs suggest potential beneficial effects for adjunctive anti-inflammatory agents in treatment of mood disorders, especially in depression. Diversity of agents and small sample sizes limited interpretation of the current review. Larger prospective studies are warranted to further elucidate the tolerability and efficacy of anti-inflammatory agents in specific diagnoses and for particular sub-groups of individuals (such as patients with high level of inflammation at baseline). Funding: This study was funded by an academic exchange award from People's Republic of China State Administration of Foreign Experts Affairs to Shandong Mental Health Centre and University of Southampton (2016/17: P152023038).

C16

'SEROTONIN SYNDROME' WITH TRAMADOL ALONE AND IN COMBINATION WITH SSRI/SNRI ANTIDEPRESSANTS

Mills S, Dept of Psychiatry, Univ of Southampton, Academic Centre, College Keep 4-12 Terminus Terrace Southampton, SO14 3DT mills.samuel.r@gmail.com

Huneke NTM(1), Baldwin DS(1)

(1) As presenting author

Introduction: The analgesic tramadol is both a mu-opioid receptor agonist and an inhibitor of serotonin and noradrenaline reuptake. It is commonly prescribed with other serotonergic agents, which is potentially hazardous, as concurrent use of two or more serotonergic drugs can precipitate potentially lethal 'serotonin syndrome'. We were interested in reviewing reports of serotonin syndrome occurring with tramadol either alone or in combination with other serotonergic agents. Method: We performed a literature search (date of last search: 27/02/17) using PubMed and MEDLINE with the following terms: ("Tramadol" and its trade names) AND ("serotonin syndrome"). We did not restrict the search by dates. Two independent researchers examined articles for eligibility. We included any case reports, case series, pharmacoepidemiological studies and exploratory studies examining serotonin syndrome with tramadol. We assessed the quality of reports using established 'diagnostic' criteria for serotonin syndrome: Sternbach's, Radomski's and Hunter's criteria. Wherever possible, we assessed the plausibility of tramadol causing the reported serotonin syndrome using Naranjo's Causality Scale. Results: After removing duplicates, our search identified 103 records: 36 met criteria for inclusion. The majority of articles were case reports (29), and there were 4 pharmacoepidemiological studies, 2 case series, and 1 exploratory study. Of the cases of serotonin syndrome described in case reports and case series (n = 34), seven occurred following ingestion of tramadol alone. The median Naranjo score for all cases was 7, which is interpreted as a 'Probable adverse drug reaction', suggesting plausible causation between tramadol and serotonin syndrome. The quality of case reports was variable, with 5 reports providing too little information to diagnose serotonin syndrome, and only 13 reports provided sufficient information to diagnose serotonin syndrome with all three proposed criteria. The results from pharmacoepidemiological and exploratory studies suggested that tramadol can be associated with serotonin syndrome. In a retrospective analysis of 125 cases of serotonin syndrome, 20 (16%) were exposed to tramadol, one of which occurred following tramadol ingestion alone. In studies of tramadol overdose, either alone or in combination with other drugs, serotonin syndrome was seen in 5-20% of cases. Conclusions: The results of our literature review suggest that tramadol can precipitate serotonin syndrome at clinically important rates, even when ingested alone. Clinicians should be aware of this potentially lethal adverse effect when prescribing tramadol. Huneke is an NIHR Academic Clinical Fellow with a supportive grant from the Research Management Committee of the Faculty of Medicine at the University of Southampton.

C17

EFFICACY AND SAFETY OF LURASIDONE IN CHILDREN AND ADOLESCENT PATIENTS WITH BIPOLAR I DEPRESSION

Goldman R, Clinical Development & Medical Affairs, Sunovion Pharmaceuticals Inc, 84 Waterford Drive, Marlborough, MA, 01752 paladinmed@gmail.com

DelBello MP(2), Deng L(1), Cucchiaro J(1), Loebel A(1)

(1) As presenting author; (2) University of Cincinnati College of Medicine, Cincinnati, OH

Introduction: Pediatric bipolar depression is a recurrent, disabling illness for which few evidence-based treatments are available. Lurasidone is approved by the FDA for the treatment of bipolar depression in adults. The aim of this multi-regional study was to evaluate the efficacy and safety of lurasidone in children and adolescents with bipolar depression. Methods: Patients ages 10-17 years of age with a DSM-IV-TR diagnosis of bipolar I depression were randomized to 6 weeks of double-blind treatment with once-daily, flexible doses of lurasidone in the range of 18.5-74 mg. Primary and key secondary endpoints were change from baseline to week 6 in the Children's Depression Rating Scale, Revised (CDRS-R) total score, and the Clinical Global Impressions, Bipolar Severity of Depression Score (CGI-BP-S), respectively, evaluated by

mixed model repeated measures analysis. Results: A total of 347 patients were randomized and received at least one dose of lurasidone (N=175; male, 50.3%; mean age, 14.2 years) or placebo (N=172; male, 51.7%; mean age, 14.3 years). Mean dose of lurasidone was 29.3 mg/d, with modal dose distribution of 51.8%, 26.5%, 12.9%, and 8.8% for 18.5 mg, 37 mg, 56 mg, and 74 mg, respectively. Treatment with lurasidone was associated with significantly greater week 6 endpoint improvement vs. placebo on the CDRS-R total score (-21.0 vs. -15.3; P<0.0001; effect size, 0.45), and the CGI-BP-S score (-1.49 vs. -1.05; P<0.0001; effect size, 0.44). Lurasidone was also associated with statistically significant and clinically meaningful improvement in secondary measures of anxiety, quality of life, and global functioning. Study completion rates were 92.0% on lurasidone, and 89.7% on placebo; discontinuation rates due to adverse events were the same (1.7%) for both groups. The 3 most frequent adverse events on lurasidone vs. placebo were nausea (16% vs. 6%), somnolence (11% vs. 6%), and increased weight (7% vs. 2%). At study endpoint, a numerical reduction was observed in median change in fasting lipid parameters; no change was observed in fasting glucose or HbA1c; and an increase was observed compared with placebo in mean weight change (+0.74 kg vs. +0.44 kg) and median prolactin (+ 1.10 vs. +0.50 ng/mL). Conclusions: In children and adolescents with a diagnosis of bipolar depression, lurasidone demonstrated statistically significant and clinically meaningful improvement on measures of depression severity, and on secondary measures of anxiety, quality of life, and global functioning. In this study, lurasidone was associated with few effects on weight and metabolic parameters, and was generally well-tolerated. Sponsored by Sunovion Pharmaceuticals Inc.

C18

THE EFFECT OF FOUR WEEKS SSRI ADMINISTRATION ON NONVERBAL BEHAVIOUR IN HIGH AND LOW NEUROTIC HEALTHY VOLUNTEERS

Di Simplicio M, Cognition and Brain Sciences Unit, MRC, 15, Chaucer Road Cambridge, CB2 7EF martina.disimplicio@mrc-cbu.cam.ac.uk

Warren MB(1), Troisi A(2), Harmer CJ(1)

(1) Department of Psychiatry, University of Oxford, Oxford OX3 7JX; (2) Department of Systems Medicine, School of Medicine, University of Rome Tor Vergata, Rome, Italy

Introduction Models of antidepressants action suggest that drugs act by reverting the cognitive biases in emotional information processing typical of psychopathology. Over time this could lead to a more functional interaction with the environment, for example affecting the way individuals interpret and express interpersonal signals (Harmer et al., 2017, Lancet Psychiatry, Jan 30). The current study tested this hypothesis by adopting an ethological approach: observing behaviour patterns during individuals' interaction with the environment, without the limitations of subjective self-report. We investigated the effect of 4-week SSRI administration on nonverbal behaviour during a dyadic interaction. As personality can influence the response to antidepressant treatment (Di Simplicio et al., 2013, Psychological Medicine 44:1–12), we also explored treatment effect differences in high and low neurotic healthy individuals. Methods 48 healthy volunteers with high (>16) and low (<5) neuroticism (N) scores on the Eysenck Personality Questionnaire (High N=24, Low N=22) were randomised to receive 4 weeks of 20mg citalopram or placebo (citalopram=24, placebo=22). At baseline and on day 28 of drug administration, participants' nonverbal behaviour during a 20 minutes interview by the same male experimenter was videotaped (i.e. participants' face and trunk without audio). Nonverbal behaviour was coded using the Ethological Coding System for Interviews (ECSI; Troisi, 1999, Neuroscience and Biobehavioral Reviews, 23:905–913) measuring 37 different behaviour patterns (facial expressions, body movement). Affect, depression and anxiety levels were also measured. Results There was no main effect of drug on change in nonverbal behaviour measures on the ECSI. However, there was a two-way interaction between neuroticism and drug group ($F(1,38)=437.7$, $p=0.03$) on change in the measure indexing low-level aggression and hostility (e.g. leaning forward, frowning). In the high neurotic group there was a significant effect of citalopram ($p=0.047$), reflecting reduced low-level hostility and aggression following SSRI treatment. There were no significant drug effects on affect, depression and anxiety levels. Conclusions These results show that citalopram can modify nonverbal behaviour during an interpersonal interaction after 4-weeks administration. This effect may represent drug-induced changes in interactions with the environment that in turn can facilitate symptoms resolution: for example expressing less hostile cues during a conversation can allow more

positive interpersonal communication and increase social support. Consistent with previous findings, our data suggest that SSRI effect differs depending on individuals' personality traits. This can improve our understanding of the variable responses to antidepressant treatment. This study was funded by a OUP John Fell Fund Small Grants Award to Martina Di Simplicio.

C19

This abstract has been withdrawn

C20

DOSE-DEPENDENT EFFECTS OF KETAMINE AND NORKETAMINE ON BRAIN PERFUSION IN HEALTHY VOLUNTEERS

de Rover M, Dept of Anesthesiology, Leiden University Medical Center, Albinusdreef 2, Leiden, The Netherlands, 2300 RC rovermde@fsw.leidenuniv.nl

van Osch MJ(2), Dahan A(1), Niesters M(1)

(1) As presenting author; (2) Dept of Radiology, Leiden University Medical Center, Leiden, The Netherlands

Introduction: Ketamine is an NMDA receptor antagonist, which is well known for its analgesic and antidepressant properties. Like many other drugs, ketamine is metabolized into active compounds which have been suggested to contribute significantly to its effects. However, human data on ketamine's main active metabolite norketamine are sparse because norketamine is not available for use in humans. Previously, we showed that ketamine affects cerebral blood flow in the human brain. We re-analyzed this dataset, using a pharmacokinetic-pharmacodynamic model, to determine the relative contributions of ketamine and norketamine on cerebral blood flow. Methods: Twelve healthy male volunteers received a 2-hr ketamine (increasing dose) or placebo infusion (crossover). Brain perfusion was measured using pseudo-continuous arterial spin labelling (PCASL) at several time points before, during and after administration. Voxel-wise cerebral blood flow was quantified in each PCASL set and registered to the MNI152 template. A pharmacokinetic-pharmacodynamic model was used to describe the estimated brain concentrations of ketamine and norketamine over time, which were then regressed against the voxelwise cerebral blood flow using randomise as implemented in FSL and corrected for multiple comparisons using threshold free cluster enhancement (tfce). Results: As previously reported the main effect of ketamine is a significant increase in cerebral blood flow in prefrontal brain areas ($p<0.01$ tfce corrected). Our pharmacokinetic-pharmacodynamic analysis showed that this increase was not specific for ketamine or norketamine: both compounds were driving this effect. Further, ketamine caused a bilateral increase in cerebral blood flow in the posterior cingulate cortex, bilateral amygdala and the thalamus ($p<0.01$ tfce corrected). The latter effects were specific for ketamine and not induced by norketamine and were significant only in the pharmacokinetic-pharmacodynamic analysis and not in the main effect analysis. Conclusions: This is the first report that couples the estimated brain concentrations of a drug and its metabolite to cerebral blood flow, via a pharmacokinetic-pharmacodynamic model. Both ketamine and norketamine increased cerebral blood flow in the prefrontal cortex. Additionally, cerebral blood flow was increased by ketamine only in brain areas that play an important role in ketamine's antidepressant and analgesic effects. No sponsorship was received for the study.

C21

THE EFFECT OF A TRANSDERMAL SCOPOLAMINE PATCH ON EMOTIONAL PROCESSING

Bukala BR, University Department of Psychiatry, University of Oxford, Warneford Hospital, OX3 7JX bernard.bukala@worc.ox.ac.uk

Browning M(1), Cowen PJ(1), Murphy SE(1), Harmer CJ(1)

(1) Neurosciences Bldg, Univ Dept of Psychiatry, Warneford Hosp, Oxford OX3 7JX

Introduction Available treatments for major depressive disorder (MDD) have limitations and there is a need for the development of more effective, rapid acting antidepressants. The cholinergic system, which plays a central role in attention and memory, has long been implicated in the pathophysiology of

depression. Scopolamine, an anticholinergic drug, has well-established disruptive effects on cognition (Ghoneim et al., 1975, Psychopharmacologia 44, 257-262); however it has also been shown to produce a robust antidepressant effect in depressed patients when administered intravenously (Furey & Drevets, 2006, Arch. Gen. Psychiatry 63, 1121-1129). The cognitive neuropsychological model of depression postulates that antidepressants exert their effect through correcting a negative emotional cognitive bias present in MDD, an effect which can also be observed in healthy participants (Harmer et al., 2003, Neuropsychopharmacology 28, 148-52). This study aimed to evaluate the effect of an openly-available transdermal scopolamine patch on emotional processing, as a cognitive biomarker of antidepressant efficacy. The study also measured the non-emotional cognitive effects of the scopolamine patch. Methods and results A scopolamine or placebo patch was administered to healthy volunteers [n=33, f=20, mean age=23.28] over 17h in a double-blind randomised procedure. Emotional cognition was assessed using the P1vital® Oxford Emotional Test Battery. In the emotional memory task, a significant group x valence (positive/negative word) interaction was observed [F(1,31)=5.652, p=0.024]. The interaction reflected relatively reduced recall of positive words combined with an increased recall of negative words in the scopolamine group. No further effects on measures of emotional memory were found, including facial expression recognition accuracy [F(1,30)=0.200, p=0.658]. Drug administration had no detrimental effect on measures of verbal memory and working memory capacity. Questionnaire baseline and state measurements were also completed and no significant differences between the groups were found. Conclusions Contrary to expectations, the scopolamine patch had no clear effects on either emotional or non-emotional cognition. The observed effect of negative bias on emotional memory is in direct opposition to the hypothesis. There are a number of possible explanations for the results, including the low effective dose of scopolamine available through the transdermal patch. Alternatively, the antidepressant effect of scopolamine might be independent of changes in emotional cognitive biases. The reasons for previous findings of cognitive impairment induced by transdermal scopolamine (Parrott, 1986, Psychopharmacology (Berl). 89, 347-354) not being replicated are unclear. Future investigation should assess the effect of higher, possibly intravenous doses of scopolamine on emotional cognition. [No external sponsorship.]

C22

A PILOT AUDIT OF ANTIDEPRESSANT SWITCHING IN A COMMUNITY MENTAL HEALTH TEAM.

Hodgson RE, Psychiatry, Lyme Brook Centre, Newcastle u Lyme Staffordshire, st15 8JN rhod819147@aol.com

Eboka YM(1)

(1) As presenting author

Introduction Switching antidepressants may be necessary due to poor efficacy, side effects, interactions, patient choice or physical health concerns. The Maudsley Prescribing Guidelines 12th Edition (MPG) highlights the risk of withdrawal phenomena and advises against abrupt discontinuation when antidepressants are taken continuously for six weeks or longer unless a serious adverse event has occurred. Tapering may reduce the risk of discontinuation symptoms but the co-administration of some antidepressants even when cross tapering is contraindicated due to increased risk of adverse events. In some cases cross tapering may not be considered necessary. Much of expert advice is theoretical rather than clinical evidence based. Using MPG as a standard we audited switching in a CMHT. Method Following asmall trial of the audit proforma we audited a random sample of notes to ascertain 30 sets for patients who had been on antidepressant medication for six weeks or longer and had a switch between 1st of January 2016 and 31st of December 2016. Results All switches were successful with no reported adverse effects. Lack of efficacy, side effects and patient request were the primary reasons for switches with lack of efficacy being the most common reason (80%). 83% of switches were in line with guidelines. Abrupt switches which were successful include mirtazapine 45mg to venlafaxine 37.5 mg, citalopram 40mg to mirtazapine 15mg and fluoxetine 60mg to venlafaxine 37.5mg (all total daily dose). The rationale for choosing the new medication was documented in 20% of cases. 63% of cases had been ill for more than five years, 20% for two to five years and 17% for less than a year and. 60% of cases had been on one or two previous antidepressants whereas 16.7% had been on four or more. The primary diagnoses included depression (50%) and mixed anxiety/depression (23.3%). Other diagnoses included OCD, PTSD, GAD,

dysthymia and bipolar affective disorder. The length of switch ranged from seven days to six weeks. Conclusions Our small pilot audit demonstrates switching antidepressant is not associated with significant issues despite some cases demonstrating non adherence to published guidelines. Clinicians however need to be aware of associated risks and should where possible follow guidelines. However, published guidelines are not robustly evidenced based and more audit and real world data (observational) needs to be collected to better inform clinicians and patients. No sponsorship received.

C23

THE EFFECTS OF ADJUNCTIVE MINOCYCLINE THERAPY IN TREATMENT RESISTANT DEPRESSION (MINDEP)

Hastings C, Psychological Medicine, IOPPN, Kings College London, The Maurice Wohl Clinical Neuroscience Institute, G.33.69, Cutcombe Road, King's College London, London, SE5 9RT caitlin.hastings@kcl.ac.uk

McLaughlin A(3), Nettis MA(3), Nikkheslat N(3), Zajkowska Z(3), Young A(1), Cleare A(2), Pariante C(3), Mondelli V(3)

(1) Centre for Affective Disorders Institute of Psychiatry, Psychology & Neuroscience (IoPPN) Room E2.10 PO72 De Crespigny Park Denmark Hill London SE5 8AF; (2) PO74 Affective Disorders 103 Denmark Hill Denmark Hill London United Kingdom; (3) The Maurice Wohl Clinical Neuroscience Institute, Cutcombe Road, King's College London, London

In recent years, there have been strong findings suggesting the role of inflammation in the development of depression. Studies have also shown that depressed patients with higher inflammation levels are less likely to respond to antidepressants (Cattaneo et al., 2013, Neuropsychopharmacology, 38, 377-385). When taken together with other evidence, this explains why there has been an increased calling for trials looking at the antidepressant effects of anti-inflammatory medication, if even in a sub-sample of the depressive population. We have decided to examine the effects of minocycline as it has a broader anti-inflammatory action than other medications such as cyclo-oxygenase (COX) inhibitors and can work on pathways involving activation of indoleamine 2,3-dioxygenase (IDO) a key enzyme in the metabolism of the serotonin precursor, tryptophan, as well as activation of the p-38 intracellular pathway, which leads to an increase in the expression and function of the serotonin transporter. The main aim of the study is to investigate association between changes in inflammatory biomarkers and improvement in depressive symptoms following adjunctive treatment with minocycline in treatment resistant depressed (TRD) patients selected for increased inflammation (Pae et al., 2008, Biomedicine &Pharmacotherapy, 62(5), 308-311; Molina-Hernandex et al., 2008, Progress in Neuro-Psychopharmacology & Biological Psychiatry, 32(2), 380-386). We have recruited 23 patients with TRD, and to date have randomised 11 patients (although 13 have been eligible). To determine eligibility, we have collected information about their current mood using the Hamilton Depression Rating Scale (HAM-D) and also about previous diagnoses using the M.I.N.I. International Neuropsychiatric Interview. Blood samples have also been taken to determine hsCRP levels. For those eligible for randomisation, we have conducted the Childhood Trauma Questionnaire (CTQ) and various other assessments at the baseline visit. Out of 22 patients, 13 have been eligible with 11 randomised and 9 excluded due to CRP being less than 1 mg/L, 2 due to an ineligible HAM-D score and 2 being excluded due to other circumstances. We have recruited 15 females and 8 males, with 3 males and 10 females being eligible for the trial, (mean age ± SEM: 44±2.08 years). Mean HAM-D at baseline was 19 (SEM±1.33) and 10 (SEM±1.92) at the final visit (with 7 patients completing the trial). The mean CTQ score is 56, with a score range of 33 to 100 in the group. This trial is still ongoing and we are hoping to complete recruitment and present the first data in the next year. Financial Sponsorship: NIHR BRC Funding.

C24

INFLUENCE OF BASELINE GABA ON REWARD PREDICTION ERROR IN HEALTHY AND DEPRESSED INDIVIDUALS

Kumar PK, Psychiatry, McLean Hospital/Harvard Medical School, Center of Depression, Anxiety and Stress Research, deMarneffe building 115 Mill Street, Belmont, MA, 02138 ak.poorni@gmail.com

Jensen JE(1), Bachetti JLB(1), Yiang JY(1), Pizzagalli DAP(1)

(1) Center of Depression, Anxiety and Stress Research, deMarneffe building 115 Mill Street, Belmont, MA

Introduction: Studies have reported that major depressive disorder (MDD) is characterized by reduced reward and increased punishment learning. Critically, animal studies have shown that dopamine (DA) signalling in the ventral tegmental area and gamma-Aminobutyric acid (GABA) transmission from the habenula, as well as interactions between these systems are implicated in reward and punishment learning. This interaction in turn modulates DA release to and GABA concentrations in the basal ganglia. Despite compelling evidence of interactions between DA and GABA systems during reinforcement learning in animals, no study has investigated these effects in humans. Methods: We collected baseline GABA levels in the left and right basal ganglia using a novel multi-voxel Magnetic Resonance Spectroscopy Imaging technique from 13 healthy controls and 12 MDD individuals. Participants then completed a social reinforcement learning task associated with social rewards and punishments whilst in the fMRI scanner. We used Q-learning algorithm to calculate reward prediction error (RPE) that was parametrically modulated with the onset times of reward feedback to identify brain regions that encode these reward prediction error (RPE) signals. Results: Consistent with the literature, preliminary findings across 9 participants showed RPE signal in the bilateral putamen ($p < 0.05$). Critically, we found a negative correlation between GABA levels and RPE in the putamen (with lower GABA associated with higher RPE, which represents better learning). Conclusions: Our preliminary findings highlight potential synergies between DA related RPE and GABA in the striatum, opening new avenues for building a working model of depression and identify novel therapeutic interventions. Funding sources: This study was funded by National Institute of Mental Health 5R21MH105775-02 and Brain and Behavior Research Foundation (formerly NARSAD) Young Investigator award, both awarded to PK.

C25

GLUTAMATERGIC SYSTEM AND DEPRESSION: AN MRS 7 TESLA STUDY IN MEDICATION-FREE DEPRESSED PATIENTS

Godlewska BR, Department of Psychiatry, University of Oxford, Warneford Lane Oxford, OX3 7JX beata.godlewska@psych.ox.ac.uk

Emir U(1), Sharpley A(2), Masaki C(2), Cowen PJ(2)

(1) FMRIB, NDCA, John Radcliffe Hospital, Oxford OX3 9DU; (2) Neurosciences Bldg, Univ Dept of Psychiatry, Warneford Hosp, Oxford OX3 7JX

Introduction - The possible involvment of the glutamatergic system in the pathophysiology and treatment of depression is of intense current interest. Proton Magnetic Resonance Spectroscopy (MRS) allows in vivo assessment of this system. Meta-analyses of MRS studies have suggested a decrese in the glutamatergic function in depression, however, most previous studies, done at magnetic field strengths of 1.5 - 3 Tesla, were not able to separately report glutamate and glutamine, which discrimination is difficult at these field strengts. The field strength of 7 Tesla allows a clear spectral resolution of glutamate and glutamine. The aim of this study was to use 7T MRS to assess glutamate and glutamine in three brain voxels, in anterior cingulate cortex (ACC), occipital cortex, (OCC) and putamen (PUT) in unmedicated depressed patients and healthy controls. Methods ¬- 55 unmedicated depressed patients and 50 matched healthy volunteers with no history or current psychiatric conditions and somatic disorders were included. All participants were scanned on a 7T whole body MR system (Siemens, Erlangen) with signals acquired from three brain voxels of interest (VOIs), in anterior cingulate cortex (ACC), occipital cortex, (OCC) and putamen (PUT). Metabolites were quantified with LCModel using the unsuppressed water signal as reference. Metabolite differences between groups and VOIs were assessed using repeated measures ANOVA and post-hoc t-tests. Results - Depressed patients showed no difference in glutamate levels compared to controls in any of the three VOIs

studied; however glutamine concentrations were increased by about 14% in PUT (p< 0.001). Glutamine was higher in depressed patients in the ACC, although the difference was not significant (p=0.07); however glutamine level in ACC positively correlated with BDI scores (r= 0.32, p= 0.025). Conclusions - These findings are of interest in view of the stipulated role of the basal ganglia in depression and in line with increased activity in the descending cortical glutamatergic innervation to the PUT. Discrepant results for the three VOIs suggest that changes in depression may not be global but restricted to regions with specific roles in patophysiology of depression. This study was funded by Medical Research Council.

C26

DISSOCIABLE TEMPORAL EFFECTS OF BUPROPION ON BEHAVIOURAL MEASURES OF EMOTIONAL AND REWARD PROCESSING IN MAJOR DEPRESSIVE DISORDER

Walsh AEL, Department of Psychiatry, University of Oxford, Neurosciences Bldg Univ Dept of Psychiatry Warneford Hosp Oxford, OX37JX annabel.walsh@psych.ox.ac.uk

Michael B(2), Drevets WC(1), Furey M(1), Harmer CJ(2)

(1) Janssen Research & Development, LLC, Penns Park, Pennsylvania; (2) Neurosciences Bldg, Univ Dept of Psychiatry, Warneford Hosp, Oxford, OX3 7JX;

Background: Previous research has shown that early in treatment, prior to an improvement in mood, serotonergic and/or noradrenergic antidepressants can remediate negative biases in information processing observed in major depressive disorder (MDD). However, it remains unclear whether dopaminergic antidepressants, such as bupropion, exert similar early actions on information processing. Here we investigate the early and longer-term effects of bupropion on behavioural measures of emotional and reward processing in MDD patients. Method: Complete data sets were obtained for 41 MDD patients and 40 healthy controls (HC). In a repeated measures study design, open-label bupropion was administered to just the MDD patients over a 6 week period. All participants completed the Emotional Test Battery and a reward task at baseline, week 2 and week 6. Results: Bupropion was found to reduce negative biases in emotional processing on the ETB early in treatment at 2 weeks. Specifically, only the bupropion-treated MDD group displayed a significant decrease in the percentage misclassification of faces as sad ($F_{1, 80} = 4.09$, $p < 0.05$; $t_{41} = 2.72$, $p < 0.05$) and the number of negative self-referent words falsely recalled ($F_{1, 81} = 5.73$, $p < 0.05$; $t_{42} = 2.12$, $p < 0.05$) between baseline and week 2. Conversely, bupropion was found to significantly worsen performance on the reward task between baseline and week 2 ($t_{14} = 4.17$, $p < 0.01$) prior to normalisation to HC levels after the full 6 week treatment ($t_{14} = -10.5$, $p < 0.001$; $t_{28} = -0.25$, $p = 0.80$). Conclusions: It appears that early in treatment, bupropion does act to reduce negative biases in emotional processing but worsens reward processing. The beneficial actions of bupropion on reward processing then occur later in treatment. Such dissociation in the temporal effects of bupropion on emotional and reward processing has implications in the treatment of the different symptom domains of negative affect and anhedonia in MDD. Conduct of the research was supported by a DPhil scholarship awarded to AELW from the Medical Research Council and by a grant awarded to CJH from J&J DPhil funding awarded to AELW by the Medical Research Council and to CJH by J&J.

C27

WISTAR KYOTO VS. SPRAGUE DAWLEY RATS IN THE DELAYED NON-MATCH TO SAMPLE TASK: EFFECTS OF KETAMINE AND PREGNENOLONE-METHYL-ETHER (PME).

Sokolowska E, Transpharmation Ireland Ltd., Trinity College Dublin - Institute of Neuroscience (TCIN) Trinity College, Dublin, Dublin 2 ewa.sokolowska@transpharmation.co.uk

McDonnell CW(1), Rouine J(1), DiCapua G(1), Prenderville JA(1), Bianchi M(1)

(1) As presenting author

Wistar Kyoto (WKY) rats are an endogenous model of TRD resistant to selective serotonin reuptake inhibitors (SSRIs) but responsive to ketamine. Pregnenolone-methyl-ether (PME), a microtubule modulator has antidepressant efficacy in rats. Here, we investigated cognitive performance in WKY rats, compared to “healthy” Sprague Dawley (SD) rats, in the delay non-match to sample (DNMS) task. The effects of PME and

ketamine in such task were also investigated in WKY rats. Ketamine was used at the single dose of 5mg/kg (s.c.) which has rapid and persistent antidepressant effects in WKY rats and mimic plasma exposure of the antidepressant dose used in the clinic (Momberau et al., SfN meeting 2015). The DNMS task was employed to assess working memory. Performance in the DNMS task was measured as total percentage correct responses (TPCR) and percent correct responses (PCR) across 6 delay periods (1-5s, 6-10s, 11-15s, 16-20s, 21-25s, 26-30s). Male (3 months) WKY (n=10) and SD (n=9) rats were used. WKY rats received a single injection of PME (10mg/kg, s.c.) and, after a period of washout (2 weeks), ketamine (5mg/kg, s.c.). Animals were recorded in the DNMS task 30 min (ketamine) 90 min (PME) and 24h (both drugs) post administration. SD rats served as ”healthy” control and received vehicle. Data were analysed using a two-way ANOVA followed by a Fisher’s LSD test. WKY rats showed impaired performance in the DNMS compared to SD; TPCR (SD: 85.80±2.59 vs. WKY: 80.53±1.38, p=0.08) and PCR delay periods: 16-20s (SD: 84.59±3.16 vs. WKY: 77.07±2.46, p<0.05) and 21-25s (SD: 80.44±4.2 vs. WKY: 72.533±3.01, p<0.05). At 30min post-treatment ketamine worsen WKY rats performance; TPCR (SD+vehicle: 86.53±2.75 vs. WKY+ketamine: 74.26±4.25, p<0.05) and PCR delay periods: 11-15s (SD+vehicle: 88.43±4.75 vs. WKY+ketamine: 73.33±8.07, p<0.05), 21-25s (SD+vehicle: 85.18±4.41 vs. WKY+ketamine: 64.44±5.62, p<0.01), and 26-30s (SD+vehicle: 78.39±5.43 vs. WKY+ketamine: 57.41±5.86, p<0.01). PME rescued WKY rats performance 90 min after administration (TPCR: SD+vehicle: 81.23±2.8 vs. WKY+PME: 83.67±2.45). Both ketamine (TPCR: SD+vehicle: 84.94±3.42 vs. WKY+ketamine: 83.33±1.77) and PME (TPCR: SD+vehicle: 85.97±2.5 vs. WKY+PME: 78.36±2.84) appears to rescue WKY performance at 24h post-treatment. WKY rats had working memory deficits in the DNMS task compared to “healthy” SD rats. Acute ketamine at the antidepressant dose of 5mg/kg (s.c.) worsened such cognitive deficits at 30min post-administration, but not at 24h. In contrast, PME confirmed to have rapid and persistent pro-cognitive efficacy (Bianchi and Baulieu, 20102; PNAS 109:1713-1718). PME show a safer antidepressant profile than ketamine. Supported by Transpharmation Ireland Ltd.

C28

RESTRAINT STRESS-INDUCED DEFICITS ON EXPLORATORY ACTIVITY ARE ATTENUATED BY FACILITATION OF 5HT7 RECEPTORS IN THE MEDIAN RAPHE NUCLEUS OF RATS.

Padovan CM, Faculdade de Filosofia, Ciências e Letras de Ribeirão Preto, Univ de São Paulo, Av Bandeirantes 3900, Ribeirão Preto, SP, Brazil, 14040-901 cpadovan@usp.br

Daher F(1), Lopes WL(2), Zuelli FMGC(2)

(1) As presenting author; (2) Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Avenida Bandeirantes 3900, 14040-900, Ribeirão Preto, SP, Brazil;

Depression has been associated to mal-functioning of the serotoninergic system. In animal models, drugs acting on the serotoninergic system such as tricyclic antidepressants and SSRIs (selective serotonin reuptake inhibitors) attenuate stress-induced effects. Recently, the 5-HT7 serotonin receptor (5HT7) was implicated in the regulation of emotional states. 5HT7 is expressed in the raphe nuclei, and in the median raphe nuclei (MnRN) it is located on glutamatergic neurons, possibly mediating the activation of the MnRN-dH pathway and interfering with stressful memories. Therefore, the aim of this work was to investigate the role of MnRN 5-HT7 on restraint stress-induced deficits on exploratory activity of an Elevated Plus Maze (EPM). All procedures were approved by the Animal Research Ethics Committee (#2014.1.231.53.9). In a first study, male wistar rats (7 weeks old) with a cannula aimed to the MnRN received an injection of LP-44 (LP; 5HT7 agonist; 0.1; 0.3 and 1.0nmol/0.2µl), SB 258741 (SB; 5HT7 antagonist; 0.03; 0.1 and 0.3nmol/0.2µl) or Saline (SAL; 0.2µl) 5 min before test in the EPM. The number of enclosed arm entries (EAE) and percentage of entries (OAE) and time spent (TOA) in the open arms were registered. In a second experiment, immediately before or after being restrained, or 24h after stress, rats received two injections of SAL, SB (0.1nmol/0.5µl) and/or LP (0.3nmol/0.5µl) combined as follows: SAL+SAL(n=9-13), SAL+LP(n=10); SB+SAL(n=8-11) and SB+LP(n=8-9). Test in the EPM occurred 24h later. Control condition included treatment 24 h before test in the EPM. After test rats were sacrificed under anaesthesia, transcardially perfused and had their brain removed for histological analysis. Data was analysed by ONEWAY ANOVA followed by Duncan test, considering significant p<0.05. Naive rats showed no differences between groups on EAE($F_{6,38}$=0.83), OAE ($F_{6,38}$=1.95) or TOA ($F_{6,38}$=1.49) (p>0.05 for all variables). Similar results were found on EAE when treatment was performed immediately before ($F_{3,33}$=0.72; p>0.05) or after ($F_{3,33}$=2.08;

p>0.05) restraint or 24h after stress (F3,32=0.81; p>0.05). However, LP increased OAE and TOA when given immediately before (OAE: F3,33=9.74; p<0.05; TOA: F3,33=9.74; p<0.05), after (OAE: F3,33=4.29; p<0.05; TOA: F3,33=8.28; p<0.05) or 24h after (OAE: F3,32=12.36; p<0.05; TOA: F3,32=8.97; p<0.05) stress, when compared to SAL+SAL. In all conditions, SB prevented the effects of LP. Intra-MnRN treatment 24h before test in naive rats did not change EAE (F3,41=0.54; p>0.05), OAE (F3,41=0.44; p>0.05) or TOA (F3,41=0.18; p>0.05). Our data suggest that activation of MnRN 5HT7 is important for adaptation to stressful situations possibly by disconnecting aversive memories. Financial Support: FAPESP (2014/20837-5; 2014/26753-8; 2013/20175-0).

C29

POSSIBLE INVOLVEMENT OF THE MAMMALIAN TARGET OF RAPAMYCIN (MTOR) SIGNALING PATHWAY IN THE ANTIDEPRESSANT-LIKE EFFECT OF AGMATINE AS A NOVEL ENDOGENOUS NEUROMODULATOR

Sahin Ozkartal C, Dept of Pharmacology and Psychopharmacology Research Unit, Marmara University Faculty of Pharmacy, Tibbiye St. No 49 Marmara University Faculty of Pharmacy Haydarpasa, Istanbul, 34668 cerenshn@gmail.com

Aricioglu F(1), Tuzun E(1), Keles R(2), Kucukali CI(1)

(1) ; (2) Istanbul University, Institute of Experimental Medical Research, Neurosciences Department, Istanbul-Turkey; (3) Sakarya University, Faculty of Medicine, Department of Pharmacology, Sakarya-Turkey

Introduction: Evidence indicates that abnormal glutamatergic neurotransmission is highly involved in depression pathophysiology. N-methyl-D-aspartate receptor (NMDAR) inhibition is potential target for fast-acting antidepressants like ketamine via the mammalian target of rapamycin (mTOR) signaling pathway (Duman et al, 2012, Neuropharmacology, 62,35-41). Recently, single administration of agmatine, an endogenous neuromodulator that blocks NMDAR, was shown to produce antidepressant-like effect similar to ketamine in chronic unpredictable mild stress (CUMS) model of mice (Neis et al, 2016, Pharmacol Biochem Behav, 150-151,108-114). However, the effect of agmatine on mTOR signaling pathway, a mechanism underlying the effects of fast-acting antidepressants, remains to be elucidated. Therefore, we addressed the effect of agmatine on mTOR activation as well as the expression of NMDAR subunits in CUMS model of depression in rats. Methods: Adult male Sprague-Dawley rats (290-320 g) were divided into 4 groups: Control and CUMS; treated with saline (0.1 ml/100 g i.p.), CUMS+Imipramine (10 mg/kg; i.p.), CUMS+Agmatine (40 mg/kg; i.p.) (n=10-12/each). In CUMS, rats subjected to series of different mild stressors (e.g. cage tilting, light/dark cycle reversal, food deprivation, swimming in hot/cold water, wet-bedding, paired-caging, etc.) in an unpredictable manner for 6 weeks. Treatments were started at third week of CUMS and continued for 21 days. Anhedonia-like behavior was assessed by sucrose preference test (SPT) in every two weeks. Finally, forced swim test (FST) was performed and prefrontal cortex (PFC) brain tissues were collected (n=7-8/each group) for real-time PCR analysis of Akt/PI3K/mTOR pathway, postsynaptic density protein-95 (PSD-95) and NR2A/NRB2B subunits . 2-ddCT calculation was used for relative quantification method. One- way ANOVA was used for FST and PCR statistical analysis whereas two-way ANOVA was conducted for SPT. Results: CUMS group rats developed anhedonia-like behavior in SPT (p<0.01) which was ameliorated by imipramine (p<0.05) and agmatine (p<0.01) treatments. CUMS+Imipramine and CUMS+Agmatine groups had shorter duration of immobility in FST compared to CUMS (p<0.001). CUMS+Agmatine but not CUMS+Imipramine had significantly higher PFC mRNA levels of mTOR (p<0.01), Akt (p<0.01), Erk1 (p<0.05), PI3K (p<0.05), NR2B (p<0.01) and PSD-95 (p<0.05) compared to CUMS. Conclusions: These results suggest that the antidepressant-like effect of agmatine may involve the activation of Akt/PI3K/mTOR signaling and increased PSD-95 as well as the modulation of NR2B subunits in PFC of stressed-rats. Our findings supporting that agmatine might have a fast-acting antidepressant potential require further investigations addressed at how acute versus chronic agmatine treatment effects region-specific changes in protein expressions of up-/downstream targets of mTOR signaling in animal depression models. Funding for this study was provided by Scientific Research Project Foundation of Marmara University (SAG-C-DRP-110915-0417).

C30

PHARMACODYNAMIC EFFECTS OF THE P2X7 RECEPTOR ANTAGONIST JNJ-54175446 IN A TRANSLATIONAL HUMAN DEXAMPHETAMINE CHALLENGE MODEL

van der Aart J, Centre for Human Drug Research, Zernikedreef 8, Leiden, Netherlands, 2333CL jaspervanderaart@gmail.com

Recourt K(1), Jacobs G(1), de Kam M(1), Khoshchin M(1), Kanhai K(1), Siebenga P(1), Zuiker Z(1), Vets E(2), Timmers M(2), de Boer P(2), van Gerven J(1)

(1) As presenting author; (2) Neuroscience Therapeutic Area, Janssen Research and Development, a Division of Janssen Pharmaceutica N.V., Beerse, Belgium

Introduction JNJ-54175446 (JNJ) is a selective, potent, brain penetrant antagonist of the P2X7 ion channel (P2X7R). The central P2X7R is involved in neural-glia interactions and activation is associated with the production of the cytokine interleukin-1β. In rodents, JNJ attenuates lipopolysaccharide/BzATP-induced increases in interleukin-1β levels and attenuates amphetamine-induced increases in locomotion. The objective of the current proof-of-mechanism study was to investigate the pharmacodynamic effects of JNJ at steady-state, using an acute dexamphetamine (AMPH) challenge as a translational model. Methods 64 healthy males (age 18-55 years) participated in a double-blind, placebo-controlled, multiple ascending dose study. 48 subjects were randomised to either JNJ (n=6 on 50 mg and 100 mg; n=12 on 150 mg, 300 mg and 450 mg) or placebo (n=16). Subjects underwent an unblinded baseline oral 20 mg AMPH challenge at day -5, followed by 11 consecutive days q.d. dosing with JNJ/placebo, with a cross-over AMPH/placebo challenge on days 7 and 10. On challenge days, the NeuroCart [Groeneveld et al.,2016, Drug Discovery Today: Technologies(20),P27-34] test battery and cortisol sampling were repeated 4 times pre- and post-challenge. A mixed model ANOVA was used with the average pre-AMPH values of day -5 as a covariate. Post-AMPH values of day -5 were subtracted from day 7/10 post-AMPH/placebo. $P<0.05$ was considered statistically significant. Results At steady state, JNJ by itself caused slight decreases of finger tapping ($p<0.04$ at 150mg and 450mg), adaptive tracking ($p<0.03$ at ≥150mg) and saccadic reaction time ($p<0.03$ at ≥150mg) compared to placebo. JNJ did not affect saccadic peak velocity, smooth pursuit eye movements, body sway or subjective effects (VAS). On day -5, unblinded AMPH stimulated a wide range of subjective and performance tests. After repetition of the AMPH challenge on day 7 or 10 in the placebo arm, AMPH effects were similar to those on day -5. JNJ ameliorated AMPH-induced increases of finger tapping ($p<0.01$ at ≥300mg) and adaptive tracking ($p=0.01$ at 300mg). JNJ enhanced subjective effects of AMPH on VAS mood ($p<0.01$ at 100mg and 150mg) and VAS feeling high ($p<0.01$ at ≥300mg). AMPH-induced cortisol elevations were also increased by JNJ ($p<0.01$ at ≥300mg). JNJ was well-tolerated at all dose levels tested. Conclusions This is the first report of the pharmacodynamic effects of the central P2X7R antagonist JNJ in humans. Similar to animal models, JNJ attenuated AMPH-induced improvements of (visuo)motor performance. Mood elevating effects of AMPH were enhanced. Overall the pattern is compatible with a potential anti-depressant effect. Funding: This study was sponsored by Janssen Research and Development, a division of Janssen Pharmaceutica N.V.

C31

MICROTUBULAR PROTEINS AS PLASMA BIOMARKERS OF KETAMINE ANTIDEPRESSANT EFFICACY – A TIME COURSE STUDY IN THE RAT

Fisher AD, Transpharmation Ireland Ltd, 3.47 Lloyd Inst, Trinity College Dublin, Dublin 2, N/A fishera@tcd.ie

Rouine J(1), McDonnell C(1), DiCapua G(1), Prenderville JA(1), Bianchi M(1)

(1) As presenting author

The N-methyl-D-aspartate receptor antagonist ketamine has shown clinical efficacy in treatment resistant depression (TRD) patients. Altered microtubule dynamics have been associated with the pathogenesis and treatment of major depressive disorder (MDD) (Bianchi and Baulieu, 2012, PNAS, 109: 1713-1718). The plasma expression of acetylated alpha-tubulin (Acet-Tub; marker of decreased microtubule dynamics) has been shown to correlate with depressive symptomatology and pharmacological intervention in Burning Mouth Syndrome (BMS), a somatoform disorder with depression comorbidity (O'Driscoll, 2016,

Journal of Psychopharmacology, 30:A64). Here, the Wistar Kyoto (WKY) rat model of TRD was used to examine the antidepressant-like effects of ketamine and the feasibility of Acet-Tub as a plasma biomarker of pharmacological efficacy. Adult male WKY rats (6-8 weeks, 200g, n=20 per group) received a single administration of ketamine (5mg/kg; s.c.) or saline (1ml/kg; s.c.). Immobility in the forced swim test (FST), a measure of depressive-like behaviour, was tested in separate groups of animals 30min, 4h, 24h and 48h post-administration. Immediately after the FST animals were sacrificed, trunk blood collected and plasma isolated for Infrared Western Blot analysis of Acet-Tub and transferrin expression. Analysis by densitometry was carried out using Odyssey software V.3. Data was expressed as percentage of control and Acet-Tub expression was normalised to transferrin. Statistical analysis was performed using a Student's t-test. Ketamine was seen to have a rapid and long-lasting antidepressant effect in WKY rats as indicated by decreased immobility in the FST 30min (saline: 67.7 ± 3.4s vs. ketamine: 55.3 ± 3.0s; $p < 0.01$) and 24h (saline: 64.9 ± 3.3s vs. ketamine: 53.2 ± 1.7s; $p < 0.01$) post-administration. No significant changes were observed at 4h post-treatment, although there was decreased basal immobility levels in saline-WKY rats at this specific time point. At 48h post-treatment ketamine lost efficacy. Acet-Tub normalised to transferrin was significantly decreased 4h (saline: 1.0 ± 0.1 vs. ketamine: 0.6 ± 0.1; $p < 0.05$) post ketamine administration. There was a significant decrease in Acet-Tub (saline: 100 ± 8.6% vs. ketamine: 74.7 ± 5.3%; $p < 0.05$) and transferrin expression (saline: 100 ± 5.0% vs. ketamine: 74.4 ± 2.2%; $p < 0.001$) 24h post-administration. Acet-Tub normalised to transferrin had a tendency towards increase at 30min, while no changes were observed 48h post-administration. This study confirmed the antidepressant efficacy of ketamine in a model of TRD, while highlighting the potential for plasma Acet-Tub expression as a biomarker of ketamine efficacy. Supported by TCD (Dept. of Physiology) and Transpharmation Ireland Ltd.

C32

MINOCYCLINE MODULATES HIPPOCAMPAL NMDA RECEPTOR SIGNALLING IN A MOUSE INFLAMMATION MODEL

Chan SY, Psychiatry, University of Oxford, Neurosciences Building, Warneford Hospital, OX3 7JX shiyu.chan@sjc.ox.ac.uk

Burnet PWJ(1)

(1) As presenting author

Drugs with anti-inflammatory properties, such as minocycline, have gained interest as possible therapeutic agents for psychiatric disorders. However, the mechanisms underlying their psychotropic properties are unclear. Studies linking the pro-inflammatory cytokine IL-1β to NMDA receptors (NMDARs) suggest that central glutamate neurotransmission may be involved.The NMDARs are associated with several signaling proteins, including extracellular signal-regulated kinase (ERK) and Calcium/Calmodulin-dependent protein kinase II (CamKII). This study, therefore explored whether NMDARs and associated signaling proteins are involved in the actions of minocycline in a mouse inflammation model. Minocycline or saline was administered to male CD1 mice for seven days, followed by a single injection of pro-inflammatory lipopolysaccharide (LPS), or saline, 24hrs before animals were sacrificed. The expression of NMDAR GluN2 subunits and ARC mRNAs in the hippocampus were determined with in-situ hybdridisation, and levels of ERK1/2 and CamKIIα were measured with western blotting. Statistical analyses were performed with two-way ANOVA or Kruskal-Wallis, and appropriate post hoc tests. LPS administration decreased GluN2B mRNA ($N=58$, -13.076%, $p<0.01$) in the CA1 region of the hippocampus. This effect was attenuated by minocycline (+20.597%, $p<0.001$), resulting in a significant minocycline x LPS interaction ($F_{1,54} = 9.968$, $p<0.01$). No significant effects were observed for GluN2A mRNA. Preliminary analysis of signalling protein levels ($N=19$) showed a significant minocycline x LPS interaction ($F_{1,15} = 29.610$, $p<0.001$) for ERK1/2. Thus, an LPS-mediated elevation of ERK1/2 compared to controls (+22.2%, $p<0.001$) was reduced by minocycline (-8.3%, $p<0.05$). Minocycline also significantly reduced CamKIIα activity compared to control ($p<0.05$) in both the presence and absence of LPS. Finally, there was a significant minocycline x LPS interaction ($N=18$, $F_{1,14} = 17.318$, $p<0.001$) for ARC mRNA at the CA1 region of the hippocampus, where its reduction by LPS was attenuated by minocycline. The actions of minocycline appear to be more strongly linked to NMDARs containing GluN2B than those containing GluN2A subunits. This is reflected by minocycline-mediated changes in CamKIIα activity, a signalling protein associated with GluN2B. Results suggest that minocycline

prevents excessive NMDAR function by either reducing CamKIIα activity or diminishing LPS-mediated increase in the ERK1/2 pathway. This altered downstream signalling is also translated to the level of neuronal activity (ARC mRNA). The reduced GluN2B expression by LPS, therefore, may be indicating a homeostatic response to increased NMDAR stimulation, which is normalised by minocycline. This study provides further evidence for the involvement of the NMDAR in inflammation and minocycline action. SYC is supported by A*STAR, Singapore.

C33

ALTERATIONS IN PLASMA CYTOKINE EXPRESSION AT BASELINE AND FOLLOWING ACUTE STRESS IN 'DEPRESSED' WISTAR-KYOTO RATS

Burke T, Transpharmation Ireland Ltd., Trinity College Dublin - Institute of Neuroscience(TCIN), Trinity College Dublin, Dublin 2 teresa.burke@transpharmation.co.uk

Prenderville J(1), McDonnell CW(1), Rouine J(1), Bianchi M(1)

(1) As presenting author

The endogenous 'depressed' Wistar-Kyoto (WKY) rat strain has been proposed as a model of treatment resistant depression (TRD) resistant to selective serotonin reuptake inhibitors (SSRIs), but responsive to a single administration of ketamine, the only efficacious drug in TRD (Tizabi et al., 2012, Neuroscience, 213:72-80). Recent research has identified a link between inflammation and depression in Major Depressive Disorder (MDD) patients (Lindqvist et al., 2017, Psychoneuroendocrinology, 76:197-205). In rodents, increased circulating cytokines have been linked to depressive-like behaviours such as anhedonia and reduced social exploration. This study assessed cytokine levels in the plasma of WKY rats and 'healthy' Sprague Dawley (SD) rats, at baseline and following acute stress induced by the Forced Swimming Test (FST). Male Sprague Dawley (SD) (3-4months; 300-350g; n =8-10 per group) and WKY rats (3-4 months; 300-350g; n = 8-10 per group) were left undisturbed (baseline) or subjected to 5 minutes of FST. Undisturbed and stressed (immediately after the FST) animals were sacrificed and plasma samples were obtained from trunk blood. Multiplexed electrochemiluminiscence detection (MSD Quickplex SQ) was used to measure plasma cytokine expression. Data were analysed using a two-way ANOVA followed by Fishers LSD test. At baseline WKY rats were found to significantly overexpress interferon-γ (WKY 2.969±0.8991 vs. SD 2.249±0.6090, $p < 0.05$) and KC-GRO (WKY 481.3±61.14 vs. SD 351.4±61.14, $p < 0.001$) in the plasma when compared to SD rats. Following acute stress (FST exposure) WKY rats now appeared to have decreased interferon-γ (WKY 6.928±0.4439 vs. SD 9.538±0.6622, $p < 0.0001$), IL-4 (WKY 4.816±0.5758 vs. SD 5.8±0.4577, $p <0.0001$) and IL-6 (WKY 27.3±8.469 vs. SD 124.7±12.65, $p <0.0001$) in the plasma when compared to SD rats. These results show that at baseline, WKY rats have higher circulating concentrations of cytokines when compared with SD rats, suggesting that the endogenous depressive-like phenotype which the WKY rat exhibits may be due in part to a dysfunctional immune system. Furthermore, following acute stress SD rats show increased plasma cytokine concentration indicative of immune system activation and this immune response appears to be blunted in WKY rats. These findings suggest that immune system dysfunction may contribute to the development of depressive-like symptoms in WKY rats. Thus the immune system may represent a novel target for antidepressant drugs while plasma cytokines may be potential biomarkers of disease progression. Supported by internal Transpharmation Ireland Ltd. funding.

C34

INVESTIGATING THE EFFECTS OF D-ALANINE ON ACTH SECRETION AND SIGNALLING PROTEINS IN ATT20 PITUITARY CELLS

Naidoo K, Psychiatry, University of Oxford, University of Oxford, Department of Psychiatry, Oxford, OX3 7JX, United Kingdom, OX3 7JX kalina.naidoo@psych.ox.ac.uk

Burnet PWJ(1)

(1) As presenting author

Background: D-alanine, an N-methyl-D-Aspartate receptor (NMDAR) co-agonist and an agonist of the strychnine-sensitive glycine receptor (GlyR), is sequestered in pituitary adrenocorticotrophic hormone

(ACTH) containing cells, but its influence on ACTH remains unexplored. Studies have shown that the CREB and ERK 1/2 signalling pathways influences ACTH secretion. The aim of this study was to test whether D-alanine modulated ACTH secretion from AtT20 cells, and the levels of signalling proteins therein. A comparative study with the NMDAR co-agonist, D-serine, was run in parallel. Methods: In the first study, AtT20 cells were incubated with D-alanine or D-serine at 100μM, 200μM and 500μM, or PBS as a control, for 24hrs. For the next set of experiments, cells were incubated with D-serine or D-alanine (500μM), followed by CRH or Dexamethasone (100nM) incubations for 24hrs. The levels of ACTH in all cell culture media was measured with ELISA, and intra-cellular CREB and ERK 1/2 levels with western blot. All data were subjected to one-way ANOVA statistics. RESULTS: An increased secretion of ACTH, and elevated intracellular tCREB (CREB/β-actin) levels were observed following a 24-hour incubation of AtT-20 cells with D-alanine (+12%, p=0.038 and +35%, p=0.011 respectively) or D-serine (+13%, p=0.043 and +29%, p= 0.028) at 500 μM. The incubation of AtT-20 cells with CRH resulted in a significant increase in ACTH levels (+17%, p=0.035) compared to PBS. Neither D-alanine nor D-serine influenced this effect. The incubation of AtT-20 cells with DEX (100nM) and D-alanine (500μM) for 24hrs, significantly decreased ACTH secretion and intra-cellular CREB (-30%, p=0.022 and -44%, p=0.03 respectively). Conversely, ACTH release from cells increased (+16%, p=0.038) when incubated with DEX and D-serine for 24 hours, increased (+16%, p=0.038). There was also a significant elevation of ERK1/2 in cells incubated with D-serine and DEX compared to the PBS group (+38%, p=0.039). DISCUSSION The increase in ACTH concentrations in the culture media of cells incubated with D-alanine and D-serine, and elevated CREB levels in AtT20 cells, suggests the activation of the NMDAR by these D-amino acids. However, in the presence of DEX, D-alanine significantly potentiated the reduction of ACTH released and intracellular CREB. In contrast, D-serine increased ACTH release and intracellular ERK1/2, but not CREB levels when cells were incubated with DEX. These data may suggest that inhibitory GlyRs are expressed in AtT20 cells in the presence of DEX, which are activated by D-alanine, and reduce CREB signalling and ACTH secretion. Studies are now underway to confirm this. I am a Commonwealth Scholar and receive a small, annual research grant towards my study.

C35

CLINICAL CORRELATES OF COGNITIVE IMPAIRMENT IN PATIENTS WITH EUTHYMIC BIPOLAR DISORDER

Guillotte C, Psych Med, IoPPN, King's College London, 103 Denmark Hill Rd London, SE5 8AZ christianne.guillotte@kcl.ac.uk

Tsapekos D(1), Strawbridge R(1), Mantingh T(1), Hodsoll J(4), Macritchie K(2), Stokes P(4), Wykes T(3), Young AH(4)

(1) 103 Denmark Hill, Psych Med, IoPPN, London, SE5 8AZ; (2) Affect Disord OPD, SLaM, London, SE5 8AZ; (3) Henry Wellcome Bldg, Psychology, IoPPN & SLaM, London, SE5 8AF; (4) Main Bldg, Psych Med, IoPPN, London, SE5 8AF

Background: Bipolar disorder is associated with a range of neurocognitive deficits that are apparent during episodes of mania and depression, and can persist during periods of recovery. These are linked to difficulties in psychosocial and occupational functioning, and subsequently reduced quality of life. The purpose of our study was to ascertain if subsyndromal symptoms of depression and/or mania are associated with poorer cognitive performance and psychosocial functioning. Methods: This study recruited 30 participants aged 18-65 with a diagnosis of bipolar disorder meeting criteria for euthymia (HDRS≤7 and YMRS≤7) at screening stage. Depression and mania severity were assessed alongside cognitive and functional outcomes. Cognitive measures comprised current IQ (WASI), verbal learning and memory (VPA), working memory (Digit Span), attention and psychomotor speed (DSST), verbal fluency (Delis-Kaplan), executive function (Hotel Test), and were summarised using a composite score. Everyday life functioning was assessed using the Functional Assessment Short Test. Results: Subsyndromal symptoms of depression (M=4.53; range: 0-11) were moderately associated with lower current IQ (r=-0.404) and higher rates of functional impairment (r=0.537). Subthreshold manic symptoms (M=2.1; range: 0-9) were not correlated with any cognitive measures. Number of current psychiatric medications was negatively correlated with immediate (r=-0.410) and delayed (r=-0.490) memory recall, and composite cognitive score

(r=-0.382). However, levels of functioning were higher in participants on an antidepressant (r=-0.450). The number of previous psychological therapies received was correlated with better functioning (r=-0.437) and slightly improved overall cognitive performance (r=0.321). Use of antipsychotics or lithium did not impact cognitive scores, although participants taking lithium were more likely to have fewer mood symptoms (r=-0.383). Anticonvulsants were the only class negatively associated with cognitive performance (r=-0.370). All reported correlations were significant at p<0.05. Conclusions: The results demonstrate that subthreshold symptoms of depression are related to poorer cognitive and daily life functioning. The direction of this association was consistent across measures. Subsyndromal manic symptom scores varied little between participants, which may have minimised any associations across these comparisons. While these results do not demonstrate causality, we suggest that more conscientious management of subsyndromal depression may improve patients' cognition and functioning. Our findings may also indicate an argument for tightening the definition of euthymia as patients experiencing symptoms in the subthreshold range may in fact be experiencing untreated illness. The cause of persistent neurocognitive dysfunction is likely multi-factorial, and pharmacological as well as non-pharmacological strategies have potential to enhance cognition and functioning in people with bipolar disorder. No sponsorship was received for the study.

C36

NEURAL ACTIVATION IN MAJOR DEPRESSION DISORDER USING A FMRI PROBABILISTIC REINFORCEMENT LEARNING TASK

Antonesei A, Centre for Integrative Neuroscience and Neurodynamics, University of Reading, Whiteknights Campus, Earley Gate, Reading, RG6 6AL a.antonesei@pgr.reading.ac.uk

Murayama K(1), McCabe C(1)

(1) As presenting author

Introduction: Anhedonia, one of the two main clinical symptoms in major depression disorder (MDD), has been experimentally related to deficits in reinforcement learning (Rizvi et al., 2016, Neuroscience & Biobehavioral Reviews, 65, 21-35). The reward deficit may point towards a dopaminergic imbalance, e.g, blunted neural activation in ventral striatum, caudate and less consistently in orbitofrontal cortex (OFC) (Dillon et al., 2014, Depression and anxiety, 31, 233-249). In a behavioural probabilistic learning task based on a differential reinforcement schedule using virtual money, MDD patients showed reduced reward learning compared to healthy controls (HC) (Pizzagalli et al., 2008, Biological Psychiatry, 57, 319-327). The aim of this study was first to adjust the reinforcement learning behavioural task to the scanner environment, and secondly to test the effects of different reinforcement ratios of rewarding taste stimuli at neural level in MDD vs HC. Methods: 59 participants (N=26 MDD, N=33 HC) took part in a probabilistic learning task inside the scanner. In a three-block event-related design, participants had to distinguish between two highly similar stimuli, while trying to maximize the intake of chocolate reward. Unknown to the participants, chocolate reward was delivered four times more for one stimulus (target) compared to the other one (non-target). Reward bias refers to the participants' tendency to define an ambiguous stimulus as target. Results: Preliminary analyses showed less BOLD activation in MDD vs. HC in the left caudate (p<.05, FWE for multiple comparisons) in response to the target vs. non-target contrasts, and in the anterior cingulate cortex (p<.05, FWE for multiple comparisons) in response to the target vs. missing the target contrasts. However, MDD vs. HC showed increased BOLD activation in the OFC/insula (p<.05, FWE for multiple comparisons) in response to the target vs. the bias contrasts. Conclusions: In line with previous research, MDD participants with anhedonia symptoms showed decreased activation to rewarding stimuli in reward areas of the brain. Moreover, MDD compared to HC showed increased OFC activation when spotting the difference between the target and the ambiguous stimulus. Results of this task showed that at the brain level, MDD compared to HC are better at differentiating between a rewarding and an ambiguous stimulus, while showing a conservative response in defining other stimuli as rewards. This work was supported by a MRC PhD scholarship.

C37

CHARACTERISING AND ENGAGING COMPUTATIONAL TARGETS RELEVANT TO DEPRESSION

Pulcu E, Dept of Psychiatry, University of Oxford, Warneford Hospital Neurosciences Building, OX3 7JX erdem.pulcu@psych.ox.ac.uk

Browning M(1)

(1) As presenting author

INTRODUCTION Negative cognitive bias, the preferential processing of negative at the expense of positive events, has been causally linked to depression. This suggests that interventions which target negative bias may reduce symptoms of the illness. Recent computational work suggests that people preferentially learn from outcomes which improve their prediction of the future (i.e. high information content). We investigated whether it was possible to introduce negative or positive biases by manipulating the information content of events in an experimental setting. METHODS Participants (n=30) completed a novel reinforcement learning task in which they were asked to choose between 2 abstract stimuli which were probabilistically associated with winning and/or losing money. The information content of wins and losses was independently manipulated in separate blocks of the task changing the volatility of their outcome probabilities. We measured how participants responded to our volatility manipulation by fitting a computational model to their choice behaviour which allows estimation of the participants' learning rates, which in turn reveals how informative people must have thought each outcome was. Using pupillometry, a physiological marker of central norepinephrine (NE) activity, we investigated the extent to which adjustments in the learning rates may be driven by the activity of the NE system. RESULTS Learning rates were significantly higher for the events (irrespective of whether they were wins or losses) which carried more information (i.e. were volatile), relative to the event which carried less information (i.e. stable; $F(1,27)=26.488$, $p<.001$). Pupils dilated significantly more for loss outcomes in the loss informative block ($F(1,27)=7.597$, $p=.01$). The differential pupil size between blocks correlated with the change in learning rate for loss outcomes ($r(28)=0.5$, $p=0.009$). CONCLUSIONS The present results indicate that people maintain separate estimates of the information content of positive and negative events, and tune their learning behaviour to track changes in the volatility of the events. Our experimental manipulation shows that it is possible to induce negative and positive biases selectively by manipulating the relative information content of different classes of event. Converging evidence from pupillometry and computational modelling of choice behaviour, particularly in the domain of loss outcomes indicate that computational methods may be used to characterise novel treatment targets. Funding Source This study was funded by a MRC Clinician Scientist Fellowship awarded to MB (MR/N008103/1).

C38

NEURAL AND CLINICAL EFFECTS OF PREFRONTAL CORTEX STIMULATION TO ENHANCE PSYCHOTHERAPY IN DEPRESSION: A DOUBLE-BLIND RANDOMIZED CONTROLLED TRIAL

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

Halahakoon DC(1), Limbachya T(2), Gray A(1), Charpentier CJ(4), Lally N(5), Aylward J(1), Pilling S(3), Roiser JP(1)

(1) As presenting author; (2) Camden and Islington NHS Foundation Trust, London WC1N 1BN; (3) Department of Clinical, Educational, and Health Psychology, UCL; (4) Department of Humanities and Social Sciences, California Institute of Technology; (5) Faculty of Medicine, University of Warwick;

Background: Transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC) has recently shown efficacy as a treatment for depression, both alone and in combination with antidepressant medication. Here we combined tDCS with cognitive behavioural therapy (CBT) to determine whether DLPFC tDCS could enhance therapeutic outcome. Methods: We conducted a double-blind randomized controlled trial of tDCS in unmedicated patients with depression receiving a course of CBT (N=39). Patients received eight 20-minute sessions of either active or sham tDCS over the left DLPFC immediately before weekly CBT. The primary outcome was the Hamilton Rating Scale for Depression (HAM-D). Secondary measures included functional magnetic resonance imaging (fMRI), measuring

DLPFC activation during working memory (N-back: 3-back>1-back contrast). We compared results from these scans with healthy controls (N=30). Our primary fMRI analysis averaged BOLD responses over our prespecified regions-of-interest (left and right DLPFC). Results: The intervention was relatively well tolerated, with 15% attrition. Using an intent-to-treat analysis (last observation carried forward), more patients responded (active: 50%; sham: 31.6%; odds ratio: 0.63) and remitted (active: 30%; sham: 10.5%; odds ratio: 0.35) following CBT with active than with sham-tDCS; however, these differences did not achieve statistical significance: (response: X2=1.37, p=0.12 (one-tailed); remission: X2=2.27, p=0.066 (one-tailed)). At baseline, patients showed DLPFC hypoactivation during the N-back compared to healthy controls (left: t(67)=2.37, p=0.02; right: t(67)=2.036, p=0.046), though significant activation was detected in both groups separately. Activation across both treatment groups increased significantly following CBT (left: t(32)=4.90, p<0.001; right: t(32)=3.50, p=0.001). Left DLPFC activation at baseline predicted change in depression (HAM-D) scores following CBT (F(1,29)=12.73, p=0.001). Crucially, there was an interaction between baseline left DLPFC activation and tDCS condition (F(1,29)=6.79, p=0.01). In patients who would go on to receive active stimulation, there was a strong association between baseline left DLPFC activation and subsequent improvement in symptoms, such that greater baseline DLPFC activation predicted a greater reduction in depressive symptoms (r2=0.504, p=0.001). This relationship was not apparent in the sham stimulation group (r2=0.04, p=0.481). Thus, heightened left DLPFC activation specifically predicted clinical response to active tDCS. Conclusions: The current findings provide support for the safety and tolerability of tDCS to augment CBT in depression. Clinical response was variable, but may be predictable: patients with higher baseline left DLPFC activation during working memory were most likely to respond to tDCS-augmented CBT. This has important implications for refining brain stimulation treatments for depression, and developing imaging biomarkers of treatment response. This study was supported by a NARSAD Independent Investigator Grant (JPR) and a Brain Research Trust PhD studentship (CLN).

C39

A RANDOMISED, CONTROLLED TRIAL ASSESSING THE EFFECT OF ACTION-BASED COGNITIVE REMEDIATION ON COGNITION AND NEURAL ACTIVITY IN BIPOLAR DISORDER AND HEALTHY FIRST-DEGREE RELATIVES

Ott CV, 6233, Psychiatric Centre Copenhagen, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, DK-2100, Copenhagen, Denmark, 2100 copenhagen caroline.vintergaard.ott@regionh.dk

Vinberg M(1), Bowie C(3), Kessing LV(1), Miskowiak KW(1), Christensen EM(2)

(1) As presenting author; (2) Copenhagen Affective Disorder Clinic, Psychiatric Centre Copenhagen, Copenhagen University Hospital, Rigshospitalet,, Edel Sauntes Allé 10, DK-2100, Copenhagen, Denmark; (3) Psychology Department, Queen's University, Kingston, Ontario, Canada

Introduction: Cognitive impairment within attention, verbal memory and executive function is present in bipolar disorder (BD) during symptomatic and euthymic states. These deficits are accompanied by aberrant neural activity in cognition-relevant neurocircuits, with hypo-activity in dorsal prefrontal regions among the most consistent findings. Cognitive impairment hampers functional recovery and contributes to lost work productivity. Prevalence of cognitive impairment is increased in patients' healthy first-degree relatives, and increases the risk of psychiatric illness onset. Currently there is no treatment targeting cognitive impairment with robust and enduring effects in BD. The aim of this trial is to assess the effect of a new form of cognitive remediation, Action-Based Cognitive Remediation (ABCR) (Bowie et al., Psychiatr. Rehabil. J. 2017;40:53–60), on cognitive impairment in patients with BD and their first-degree relatives. We will assess early treatment-associated change in neural activity within the prefrontal cortex and across the whole brain to identify a neural biomarker for pro-cognitive effects. Methods: The trial has a randomised, controlled, outcome-assessor-blind, parallel-group design. Fifty-eight partially or fully remitted patients with BD (sub-study 1) and 58 healthy first-degree relatives (sub-study 2) with objective cognitive impairment will be recruited. Participants are randomised to 10 weeks of ABCR or a control group (non-structured group sessions). Assessments are conducted at baseline, 2 weeks into treatment, immediately after treatment-completion and at a 6-month-follow-up. Participants will undergo mood ratings, neuropsychological testing, assessment of functional capacity and complete questionnaires concerning subjective cognitive complaints, psychosocial functioning and quality of life. Functional

magnetic resonance imaging (fMRI) scans are performed at baseline and 2 weeks into treatment. The primary outcome is a cognitive composite score covering verbal memory, executive function and attention. With full data sets for 52 patients and first-degree relatives, respectively, the study has a power of 80% to detect a clinically relevant between-group difference. Behavioural data will be analysed using mixed models. Functional MRI-data will be analysed with software from the FMRIB Software Library. Mean regional signal change in the dorsolateral prefrontal cortex and whole-brain analysis is analysed to investigate early treatment-related changes. Results: Results are expected in 2020. If ABCR has a pro-cognitive effect in patients with partially or fully remitted BD and/or healthy first-degree relatives, this can improve future management of BD and inspire early preventive strategies in at-risk populations. The fMRI results will provide insights into the neuronal underpinnings of ABCR-related improvements in cognition, potentially revealing key neurobiological targets for pro-cognitive interventions. The study is supported by the Lundbeck Foundation grant number: R21520154121.

C40

THE ASSOCIATION BETWEEN SLEEP AND COGNITIVE ABNORMALITIES IN BIPOLAR DISORDER

McAllister-Williams RH, IoN, Newcastle University, Wolfson Research Centre, Campus for Ageing and Vitality, Newcastle upon Tyne, NE4 5PL r.h.mcallister-williams@ncl.ac.uk

Bradley AJ(1), Gallagher P(1), Anderson KN(2)

(1) As presenting author; (2) Newcastle upon Tyne Hospitals Trust, Newcastle

INTRODUCTION Bipolar disorder (BD) is associated with a range of cognitive dysfunctions which may relate to underlying attentional and processing speed abnormalities (Gallagher et al. 2014 Psychological Medicine 44:961-74). Sleep disruption can cause attentional abnormalities and are a common feature of all stages of BD including euthymia. There is a lack of data describing the association between objectively measured sleep abnormalities and cognitive function in BD. METHODS BD patients in any mood state (n=46) and healthy controls (n=42) were assessed with 21 days of actigraphy and mood rating scales. Sleep apnoea was assessed with respiratory sleep studies. Sleep phenotypes were identified including short sleepers (<6 hours sleep per night), long sleepers (>10 hours sleep per day) and those with circadian rhythm disorders (Bradley et al. 2017 Psychological Medicine. Feb Epub). Cognitive function was assessed with a range of tasks including the Psychomotor Vigilance Test (PVT) and Attention Network Task (ANT) to assess attention and the Digit Symbol Substitution Test (DSST) to assess processing speed. BD participants with normal and abnormal sleep phenotypes were compared to controls. RESULTS BD patients had longer mean reaction times (RT) ($p<0.001$) and committed more lapses (RT >500ms, $p=0.001$) on the PVT, and had longer RTs on the orientating and conflict components of the ANT ($p<0.05$) compared to controls. Ex-Gaussian analysis of RTs demonstrated greater intra-individual variability in BD patients. BD patients also performed worse than controls on the DSST ($p<0.001$). BD normal sleepers only differed from controls on the orientating component of the ANT ($p=0.03$) but not on any other measure. BD abnormal sleepers, including just those in remission, had slower mean RT and committed more lapses than controls ($p<0.01$) on the PVT, had longer RTs on the conflict component of the ANT ($p<0.001$ for all abnormal sleepers, $p=0.077$ for those in remission), had greater intra-individual variability in RTs ($p<0.005$) and performed worse on the DSST ($P<0.05$) than controls. Sample sizes precluded quantitative comparison between different abnormal sleep phenotypes but qualitatively there appeared to be no difference between them. CONCLUSIONS This cohort of BD patients demonstrated poorer cognitive function than age and gender matched controls in expected domains and measures. These differences appeared to be driven almost entirely by the BD patients with objectively identified abnormal sleep. Mechanisms underlying the identified association between sleep and cognitive abnormalities in BD, and the impact of therapeutic interventions targeted at sleep, warrant further investigation. No sponsorship received.

C41

RESPONSES TO SOCIAL FEEDBACK IN INDIVIDUALS WITH DEPRESSION SYMPTOMS

Frey AL, Psychology Dept, Univ of Reading, Harry Pitt Building, Reading, RG6 7BE anna-lena.frey@pgr.reading.ac.uk

Cooney S(1), Copeman B(1), McCabe C(1)

(1) Univ of Reading, Psychology Dept, Harry Pitt Building, Reading RG6 7BE

Introduction: Depression is associated with social withdrawal, and it has been suggested that an increased expectancy of social rejection in individuals with depression symptoms may lead to disengagement from social situations (Kupferberg et al., 2016. Neuroscience & Biobehavioral Reviews, 69, 313-332). The current study examined whether learning or social feedback expectancies differ between individuals with high and low depression scores, and how these measures relate to reports of real-life social interactions. Methods: Forty participants with high scores (>17, HD; M age=25 years) and 52 participants with low scores (<7, LD; M age=24 years) on the Beck Depression Inventory performed a task in which they chose repeatedly between items that had different probabilities of yielding positive or negative feedback. In the non-social condition, the feedback consisted of winning or losing small amounts of money. In the social condition, the feedback was constituted of 'like' or 'dislike' signs which participants thought came from other current task players. In reality, all feedback was computer-generated. In the middle and at the end of each condition, subjects rated how likely they thought it was that they would receive positive or negative feedback when selecting a given item. Additionally, participants completed a questionnaire regarding their social relationships in everyday life. Results: Mixed measure ANOVAs revealed that, across both conditions, HD individuals' reaction times were significantly slower than those of LD participants ($p=0.004$). Moreover, there was a significant valence by group interaction for feedback expectancy ratings ($p=0.022$): HD participants expected to receive significantly more negative ($p=0.003$) and numerically less positive feedback than LD subjects. Additionally, there was a significant negative correlation ($p = 0.014$) between expectancies of receiving negative social feedback in the task and amounts of time spent with close friends in real life. Conclusion: HD participants show deficits in learning from both social and non-social feedback and have a negative bias in their feedback expectancies, which is associated with a reduction in the amount of time they spend with their close friends. Thus, the increased anticipation of negative social evaluation in HD subjects may contribute to the disengagement from close social relationships. This, in turn, could prevent exposure to future positive social interactions and exacerbate social withdrawal and depressive symptomatology. This study was funded by the MRC PhD studentship of Anna-Lena Frey.

C42

IMPACT OF MATERNAL HISTORY OF CHILDHOOD ABUSE ON NEONATAL SOCIAL INTERACTION: THE MEDIATING ROLE OF FOETAL DEVELOPMENT

Sawyer K, SPI Lab, Psychological Medicine, IoPPN, King's College London, The Maurice Wohl Clinical Neuroscience Institute Cutcombe Road, London, SE5 9RT kristi.sawyer@kcl.ac.uk

Sethna V(2), Conroy S(2), Pawlby S(2), Sundaresh S(3), Biaggi A(2), Hazelgrove K(2), Osborne S(1), Pariante CM(1)

(1) As presenting author; (2) IoPPN, KCL, 16 De Crespigny Park, London, SE5 8AF; (3) SLaM NHS Foundation Trust, King's College Hospital, London

Introduction: Maternal history of childhood abuse is linked to poor neonatal development. So far, neonatal developmental has been restricted to outcomes such as birth weight and attachment security. However, neonatal social development has not been studied in detail. This is an important omission, given its association with social development in later life. One mechanism of risk transmission may be foetal growth, which is estimated at ultrasound using four measures: one of which is biparietal diameter. This study therefore has two specific aims: to investigate the impact of maternal childhood maltreatment on neonatal social development, and to study foetal growth through biparietal diameter as a mediator of this relationship, in the context of antenatal depression. Methods: History of abuse (exposure) was measured in 150 pregnant women, using the Childhood Experience of Care and Abuse Questionnaire. Social interaction of neonates (outcome) was measured using Brazelton's Neonatal Behavioral Assessment Scale at 6 days

post-birth. Foetal biparietal diameter (mediator) measurements were obtained at the anomaly scan (20+/-3 weeks). Maternal antenatal depression (moderator) was assessed using the Structured Clinical Interview for DSM-V. An independent samples t-test was used to compare neonatal mean social orientation scores between abused and non-abused mothers. A moderated mediation model was tested using the PROCESS macro, to examine the conditional indirect effect via biparietal development, in the presence and absence of maternal antenatal depression. Results: 70 out of 150 women (45.7%) had experienced some form of childhood maltreatment. Infants born to mothers exposed to childhood maltreatment had significantly lower social orientation scores [mean=6.15(SD=1.65)] than those born to mothers who had no experience of maltreatment[7.26(1.32)], [t(144)=-4.41, p<0.001]. Where infant age, gender, and birth weight, and maternal social functioning were covariates, the direct effect of exposure to childhood maltreatment on offspring social orientation scores was significant [B=-0.97 (95% CI -1.52;-0.42)]. The mediated association via biparietal development was also significant, but only in the presence of maternal antenatal depression [B=-0.24 (-0.62;-0.04)]. Conclusions: These data indicate that foetal growth mediates, at least partially, and in the presence of antenatal depression, the negative impact that maternal experience of childhood maltreatment has on neonatal social interactivity. This suggests that neonates of mothers exposed to maltreatment are showing poor social development as early as 6 days post-birth. However, only in those exposed to antenatal depression is the association mediated by biparietal development. Sources of Financial Sponsorship: Ms Sawyer is funded by an MRC Doctoral Training Programme Studentship, at King's College London.

C43

ANTENATAL DEPRESSION IMPAIRS MOTHER-INFANT INTERACTION AT 12 MONTHS

Bind RH, Psychological Medicine, King's College London, The Maurice Wohl Clinical Neuroscience Institute Cutcombe Road London, SE5 9RT rebecca.bind@kcl.ac.uk

Biaggi A(2), Hazelgrove K(2), Osborne S(1), Fantini E(1), Conroy S(2), Sethna V(1), Pawlby S(2), Pariante CM(1)

(1) As presenting author; (2) Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London SE5 8AF

Introduction: Postnatal depression is associated with reduced mother-infant synchrony; however, it is not well established whether antenatal depression can have the same consequences. This study examined the effects of antenatal depression on mother-infant interaction at one year. Methods: This sample included 53 mother-infant dyads, 29 of whom were healthy controls (mean age = 31.7 years) and 24 of whom experienced major depressive disorder (MDD) at any point during their pregnancy (mean age = 30.7 years). A diagnosis of MDD was made if a participant met criteria for MDD on the Structured Clinical Interview for DSM Disorders (SCID) at 25 weeks gestation. Three-minute videos were recorded of each participant and infant at 12-months postpartum, for which mothers were instructed to interact with their baby as they typically would. Videos were blindly rated using the CARE-index, a reliable method for scoring mother-infant interactions, and were assessed for levels of: dyadic synchrony, maternal sensitivity, maternal control, maternal unresponsiveness, infant cooperation, infant compulsiveness, infant difficulty, and infant passiveness. Results: Compared with controls, mothers who experienced antenatal depression exhibited impaired mother-infant bonding. This was observed through: lower mean dyadic synchrony scores (5.50 vs 8.28, p<0.01), a measure of how in tune the mother and infant are with each other; lower levels of maternal sensitivity (5.63 vs 8.45, p<0.01), a measure of how pleasantly responsive a mother is to her baby; higher levels of unresponsiveness (5.25 vs 3.07, p<0.05), a measure of how withdrawn a mother is from her baby; and lower levels of infant cooperation (5.13 vs 7.41, p<0.05), a measure of how responsive a baby is to its mother's actions. There were no significant differences in maternal control, infant compulsiveness, infant difficulty, and infant passivity. Socioeconomic status and presence of postnatal depression in our participants were controlled for and did not impact our findings. Conclusions: Antenatal depression has lasting effects beyond pregnancy, as it significantly increases the risk of impaired mother-infant bonding via decreased maternal sensitivity, increased unresponsive behaviour, and as a result decreased infant cooperation and reduced overall dyadic synchrony. Sources of financial sponsorship: NIHR Biomedical Research Centre at South London and Maudsley NHS Trust and King's College London.

C44

ANTENATAL DEPRESSION AND MENTALIZATION IN MOTHER-INFANT INTERACTION AT 12 MONTHS

Allegri B, Psychological Medicine, Institute of Psychiatry, Psychology, and Neuroscience, The Maurice Wohl Clinical Neuroscience Institute Cutcombe Road London, SE5 9RT beatrice.allegri@kcl.ac.uk

Sethna V(1), Bind R(1), Mattock H(1), Tomasetti L(1), Biaggi A(1), Hazelgrove K(1), Osborne S(1), Fantini E(1), Conroy S(2), Pawlby S(2), Pariante CM(1)

(1) As presenting author; (2) Institute of Psychiatry, Psychology, and Neuroscience 16 De Crespigny Park, Camberwell, London SE5 8AF

Introduction: A mother's capacity to treat her infant as a mental agent (a process called 'mentalization') is critical for offspring development. While it is fairly well known that postnatal depression affects maternal mentalizing capacity, only limited small studies have focused on antenatal depression. The present study examines the effect of antenatal depression on maternal ability to treat her infant as a mental agent, as well as to attribute intent to her infant's vocalisations, emotions, cognitions and behaviour during face-to-face mother–infant interactions at one year. Methods: This sample included 20 mother-infant dyads, 10 of whom were healthy controls and 10 of whom were mothers who experienced major depressive disorder (MDD) at any point during their pregnancy. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) was used in order to obtain a diagnosis of MDD at 25 weeks gestation. In order to assess mentalization, mothers were instructed to play with and talk to their infants as they would normally do; a three minute video of this interaction was recorded for each mother-infant dyad. Videos were blindly rated using the The Paternal Cognitive Attributions and Mentalizing Scale (PCAMs), a reliable method which assesses maternal speech during mother-infant interactions and incorporates specific mentalization categories from the construct of 'mind-mindedness.' The two groups of mothers were compared for the following variables of interest: 1) the proportion of mentalizing comments in the total speech and 2) the focus of speech, i.e. parent-focussed or infant-focussed. Results: Antenatal depression in mothers was associated with the presence of more cognitive statements (7.45 vs. 13.55, $p<0.05$) and more infant internal statements (7.40 vs. 13.60, $p<0.05$), indicating that mothers who suffered from antenatal depression are more likely to utilize mentalizing speech. Despite these results, mothers with antenatal depression were less responsive to infant vocalizations (7.20 vs. 13.80, $p<0.05$). The educational level and presence of postnatal depression in our participants were controlled for and did not impact our findings. Conclusions: These results do not replicate previous findings in literature, which suggest mothers who experienced antenatal depression are more inclined to misinterpret the child's intent and experience. Examining parental cognitive comments may help to better understand the compensatory skills of mothers who suffered from antenatal depression, so that they remain able to respond appropriately to their infants' signals. In addition to the small sample size, further testing is needed as the PCAMs method does not assess infant behaviour, which may affect maternal use of mentalizing and directive speech. Sources of financial sponsorship: NIHR Biomedical Research Centre at South London and Maudsley NHS Trust and King's College London.

C45

CHRONIC PAIN AS A FACTOR THAT MAY WORSEN DEPRESSIVE DISORDER

Menezes IC, Dept Psychol and Education., FFCLRP, USP, Prédio Saúde Mental Av. Tenente Catão Roxo, 2650 Ribeirão Preto - SP - Brasil, 14051-140 itianacmenezes@gmail.com

Macedo BBD(1), Baes CVW(2), Juruena MF(3)

(1) As presenting author; (2) Dept Neurosc and Behav Sciences, FMRP, USP; (3) Dept Psych Med, IoPPN, KCL/ Dept Neurosc and Behav Sciences, FMRP, USP

Introduction: Comorbidity between pain and depression has been studied for decades and it has been considered a public health problem (Fishbain et al., 1997, The Clinical journal of pain; 13(2): 116-137). As literature shows, psychosocial factors, as stress and severity of depressive symptomatology, can be taken as important keys to understand the influence of chronic pain manifestation in depressive patients (Flor & Turk, 2012, J. Can. Anesth, 59:509–510). Aim: To assess if pain is associated with more severe depressive

symptoms in depressed patients. Methods: The sample was composed by N=38 patients allocated in two groups – depressive patients without chronic pain (n=18) and depressive patients with chronic pain (n=20). For depressive diagnostic assessment, MINI International Neuropsychiatric Interview was used. Previous diagnosis by health care professionals was considered for patients with chronic pain. To assess the intensity of depressive symptoms, GRID-Hamilton Depression Rating Scale (GRID_HAM-D) was applied. Results: There was no significant difference in gender (t=-0.14; p= 0.89) or age (t=-1.41; p=0.167) between the groups. Although, the mean values obtained by the total scores of GRID-HAM-D were significant higher (t=-2.39; p=0.02) in depressive patients with pain (m=24.05; sd= 4.85) than in those without pain (m=20.05; sd=4.21). Conclusion: Depressive symptoms are more severe in depressive patients with chronic pain than in those without pain. Hence, it would be interesting to consider pain as a factor that may worsen the depressive disorder. Financial Support: CAPES, FAEPA, FAPESP, and Academy Medical Sciences/Royal Society.

C46

IMPACT OF MOOD DISORDER ON CARDIOVASCULAR OUTCOMES FOR INDIVIDUALS WITH HYPERTENSION: PROSPECTIVE STUDY IN UK BIOBANK

Graham NA, Mental Health and Wellbeing, University of Glasgow, 1st Floor, Admin building Gartnavel Royal Hospital 1055 Great Western Road Glasgow, G12 OXH Nicholas.Graham@glasgow.ac.uk

Ward J(2), Ward DJ(2), Padmanabhan S(3), Cavanagh J(2), Pell J(1), Mackay D(1)

(1) 2Institute of Health and Wellbeing, University of Glasgow, Public Health, 1 Lilybank Gardens, Glasgow G12 8RZ; (2) As presenting author; (3) Institute of Cardiovascular and Medical Sciences, British Heart Foundation Glasgow Cardiovascular Research centre, University of Glasgow, Glasgow G12 8TA

Introduction Hypertension and mood disorder (bipolar disorder and depression) commonly co-occur and may share pathophysiological pathways. Both are risk factors for ischaemic heart disease but few studies have assessed whether they have an interactive effect on cardiovascular outcomes (Hamer et al. 2010 J Hypertens.;28:2401-2406, Axon et al 2010 Am J Hypertens.;23:30-37), however these studies do not adjust for psychotropic medication use. We aim to assess whether a history of mood disorder in middle-aged individuals with hypertension impacts on medium-term cardiovascular disease outcomes. Methods UK Biobank participants (n= 137,371) without cardiovascular disease were linked prospectively to hospital records and death certification over a median follow-up of 63 months (715880.16 cumulative years of follow up). Four mutually exclusive groups were compared: hypertension only (n= 56,052), mood disorder only (n = 16,393), comorbid hypertension plus mood disorder (n= 14,104), and an unaffected (no hypertension, no depression) comparison group (n=50,822). Cox proportional hazards regression was used to calculate hazard ratios (HRs) for adverse cardiovascular outcomes, adjusted in a stepwise manner for sociodemographic, health and lifestyle features. Results Adjusted HRs for adverse cardiovascular outcomes were increased for the hypertension only group (HR= 1.36, 95%CI 1.22- 1.52, $p<0.001$) and for the comorbid hypertension plus mood disorder group (HR=1.64, 95%CI 1.44-1.87, $p<0.001$). The relative excess risk due to interaction at baseline was also significant (RERI= 0.492= 95%CI 0.204 - 0.780,), and results were found to be the same during sensitivity analysis excluding those on psychotropic medication. Conclusions Individuals in middle age with hypertension/mood disorder comorbidity may require more active intervention to improve cardiovascular outcomes. Future cardiovascular risk prediction tools may benefit from the inclusion of questions about prior history of depressive disorders. The study was funded by the Aitcheson family bequest.

C47

DEPRESSIVE SYMPTOMS ARE MORE SEVERE IN PATIENTS WITH CHRONIC PAIN

Juruena MF, Dept Psych Med, Centre for Affective, IoPPN, KCL, Room E2.08 PO72, De Crespigny Park Denmark Hill, London, SE5 8AF mario.juruena@kcl.ac.uk

Macedo BBD(2), Menezes IC(1), Baes CVW(1)

(1) Dept of Neurosciences and Behavioural, University of Sao Paulo; (2) Dept Psychology and Education, University of Sao Paulo

Background: Comorbidity between pain and depression has been studied for decades, and it has been considered a public health problem (Fishbain et al., 1997, The Clinical journal of pain; 13(2): 116-37). As literature shows, psychosocial factors, as stress and severity of depressive symptomatology, can be taken as important keys to understanding the influence of chronic pain manifestation in depressive patients (Flor & Turk, 2012, J. Can. Anesth, 59:509-10). Aim: Assess if the pain can make the depressive symptoms more severe when in depressive patients. Methods: The sample was composed of N=38 patients allocated into two groups – depressive patients without chronic pain (n=18) and depressive patients with chronic pain (n=20). For depressive diagnostic assessment, MINI International Neuropsychiatric Interview was used. The previous diagnosis by health care professionals was considered for patients with chronic pain. To assess the intensity of depressive symptoms, GRID-Hamilton Depression Rating Scale (GRID_HAM-D) was applied. Results: There was no significant difference in gender (t=-0.14; p= 0.89) or age (t=-1.41; p=0.167) between the groups. Although, the mean values obtained by the total scores of GRID-HAM-D were significant higher (t=-2.39; p=0.02) in depressive patients with pain (m=24.05; sd= 4.85) than in those without pain (m=20.05; sd=4.21). Conclusion: Depressive symptoms are more severe in depressive patients with chronic pain than in those without pain. Hence, it would be interesting to consider pain as a factor that may worsen the depressive disorder. Financial support from Academy Medical Sciences/Royal Society, CAPES, FAPESP and FAEPA.

C48

THE PRESENCE OF EARLY-LIFE STRESS AND ITS SUBTYPES RAISES THE SUICIDE IDEATION SCORES OF BIPOLAR PATIENTS WHEN COMPARED TO UNIPOLAR PATIENTS

Menezes IC, Dept Neurosc and Behav Sciences, FMRP, USP, Prédio de Saúde Mental USP Av. Tenente Catão Roxo, 2650 - Monte Alegre Ribeirão Preto - SP - Brasil, 14051-160 itianacmenezes@gmail.com

Baes CVW(1), Macedo BBD(4), Cleare AJ(2), Young AH(2), Juruena MF(3)

(1) Dept Neurosc and Behav Sciences, FMRP, USP; (2) Dept Psych Med, IoPPN, KCL; (3) Dept Psych Med, IoPPN, KCL/ Dept Neurosc and Behav Sciences, FMRP, USP; (4) Dept Psychol and Education, FFCLRP, USP

Introduction:Patients with bipolar disorder present higher suicide ideation than patients with other psychiatric disorders (MANN JJ, 2002, Ann Intern Med.; 136:302-311). Over their lifetime, the vast majority of psychiatric patients with bipolar disorders have either suicidal ideation or ideation plus suicide attempts (VALTONEN H et al., 2005, J Clin Psychiatry; 66(11):1456-1462). Reports of the prevalence of suicidal ideation vary from 14% to 59% in bipolar samples (ABREU LN et al., 2009; Rev Bras Psiquiatr.; 31(3):271-280). Exposure to early life stress (ELS) may lead to a greater susceptibility of developing depression (CARR CP et al., 2013, J Nerv Ment Dis.; 201(12):1007-1020), as well as increase suicidal ideation (ABREU LN et al., 2009; Rev Bras Psiquiatr.; 31(3):271-280). ELS present some subtypes that must be considered – emotional (EA), physical (PA) and sexual (SA) abuses, and emotional (EN) and physical (PN) neglect. Aim: To assess if the presence of ELS and its subtypes influence in suicidal ideation when comparing unipolar and bipolar depressive samples. Methods: The sample was composed by two groups - unipolar depression (n=52 - without ELS= 25; with ELS= 27) and bipolar depression (n=76 – without ELS=30; with ELS=46). For diagnostic assessment, MINI International Neuropsychiatric Interview was used; to assess ELS, Childhood Trauma Questionnaire was applied; to assess suicidal ideation Beck Suicide Inventory was applied. Results: The mean scores of bipolar sample for suicide ideation was significant higher than unipolar as follow: for the presence of ELS, 2.72 times higher (t= -3.912; p<0.001); for EA, 3.43 times higher (t= -4.861; p<0.001); for PA, 3.18 times higher (t= -3.914; p<0.001); for SA, 2.57 times higher (t= -2.686; p=0.011); for EN, 4.32 times higher (t= -4.484; p<0.001); and for PN, 4.01 times higher (t= -4.038;

p<0.001). Conclusion: Considering both unipolar and bipolar groups exposed to ELS, bipolar depressed patients present a significant higher suicidal ideation than unipolar depressed patients. Financial Support: Financial support from Academy Medical Sciences/Royal Society, CAPES, FAPESP and FAEPA.

D01

TRACKING BEHAVIOURAL CHANGES FOLLOWING INDUCTION OF OLFACTORY BULBAR A-SYNUCLEINOPATHY IN MICE

Travaglio M, Translation and Integrative Neuroscience, Eli Lilly, Erl Wood Manor, Eli Lilly & Co. Ltd., Sunninghill Road, Windlesham., GU20 6PH mbymt2@nottingham.ac.uk

Blackmore T(1), Loomis S(1), Eaton J(1), Gilmour G(1), Marston H(1)

(1) Translational & Integrative Neuroscience, Erl Wood Manor, Eli Lilly & Co. Ltd., Sunninghill Road, Windlesham, GU20 6PH, UK

Introduction: In Parkinson's Disease, post-mortem studies have suggested the progressive occurrence of Lewy pathology as being key to pathogenesis. Lewy bodies contain misfolded α-synuclein, which is hypothesised to seed aggregation of natively unfolded α-synuclein before propagating and triggering sequential involvement of other vulnerable brain regions. Due to their postulated early involvement in disease, anterior olfactory structures have emerged as putative induction sites of experimental interest, where the retrograde spread of pathology into deeper mesencephalic structures may be accompanied by specific functional changes. Methods: It was hypothesized that injection of synthetic recombinant mouse α-synuclein fibrils into the olfactory bulb (OB) of twelve A53T transgenic mice would lead to the development of progressive synucleinopathy coupled to the emergence of deficits in olfactory processing. The effects of uni- (n=6) and bi-lateral infusions (n=6) at 1,2 and 3 months following fibril infusion were compared in male and female mice in two tests of spontaneous olfactory behaviour: Buried Pellet and Olfactory Dishabituation. In both experiments, odour exploration was defined as cumulative time spent sniffing while the nose was within 2 cm of the odour source. In the buried pellet test, the latency to dig and retrieve a piece of palatable food was measured using a stopwatch and compared across each time point using a Two-way ANOVA. In order to reduce experimenter bias and timing errors in the habituation paradigm, we adopted a system to automatically record exploratory behaviours using the Noldus behavioural tracking system. The mean investigation time for each trial of habituation and discrimination phases was analysed by one-way ANOVA with repeated measures across trials for each group and time point. Multiple comparisons were performed using a Tukey's post-hoc test. Results: Both uni- ($p<0.0001$) and bilateral ($p<0.01$) bulbar injection of α-syn fibrils resulted in progressive impairments in olfactory habituation in male mice, with a complete abolition of dishabituation by 60 days post infusion (unilateral: $p<0.001$, bilateral: $p<0.01$). No evidence of altered pellet detection or change in locomotor activity was recorded during this period in both gender groups ($p>0.05$). While there was tentative suggestion of sex differences in the dishabituation test, this requires confirmation in future studies. Conclusions: This pilot study demonstrated that α-synuclein may be involved in the pathogenesis of olfactory dysfunction in an experimental mouse model. Injection of α-synuclein fibrils into A53T mouse OB may recapitulate prodromal features of disease pathology of significant value to drug discovery efforts. The work was conducted during an undergraduate placement student appointment at Eli Lilly & Co. Ltd.

D02

INDUCTION OF CACNA1C HYPOFUNCTION IN KETAMINE-ACTIVATED BRAIN NETWORKS IMPAIRS MEMORY CONSOLIDATION AND ALTERS CEREBRAL METABOLISM

Dawson N, Division of Biomedical and Life Sci., Lancaster University, Faculty of Health & Medicine Lancaster University Lancaster, LA1 4YQ n.dawson1@lancaster.ac.uk

Hughes R(1), Willi C(1), Whittingham-Dowd J(1), Bristow G(1)

(1) As presenting author

Introduction: Multiple studies have identified the CACNA1C gene as a risk factor for bipolar disorder and schizophrenia. Polymorphisms in CACNA1C also influence the cognitive deficits seen in patients.

Subanaesthetic ketamine treatment induces schizophrenia-like symptoms, suggesting that ketamine modulates activity in the brain networks underlying these symptoms in patients. To further elucidate the role of Cacna1c in cognition and brain function we assess the impact of Cacna1c hypofunction in ketamine-activated brain networks on locomotion, learning and memory and cerebral metabolism. Methods: FosCreER mice, with oestrogen-regulated Cre-recombinase linked to Fos gene expression, (Guenthner et al., 2013. Neuron 78:773) were crossed with loxP-Cacna1c mice (Seisenberger et al., 2000. J Biol Chem. 275:39193). Control mice were heterozygous for FosCreER and wild-type for Cacna1c. Experimental (Cacna1c-Hypo) mice were heterozygous for FosCreER and loxP-Cacna1c. Animals were treated with 150mg/kg Tamoxifen and a subanaesthetic dose (25mg/kg) of ketamine. Locomotor activity and anxiety-like behaviour were assessed, 7 days after treatment, in the open field. Recognition memory was assessed, 8 and 9 days after treatment, using the novel object recognition test (NORT) with a 1 and 24 hour delay. Cerebral metabolism was assessed 10 days after treatment using 14C-2-deoxyglucose functional brain imaging. Group sizes were control n=11 (5 male, 6 female) and Cacna1c-Hypo n=14 (5 male, 9 female) and data were statistically analysed using ANOVA with post-hoc Tukey's HSD. Results: Cacna1c-Hypo mice showed hypolocomotion, as evidenced by a reduction in total distanced moved ($p<0.01$) and movement duration ($p<0.001$), but no significant alteration in anxiety-like behaviour (time in centre zone, $p=0.277$). In the NORT at 1 hour after acquisition both Cacna1c-Hypo and control mice showed a significant preference for the novel object ($p<0.001$). However at 24 hours after acquisition while control animals showed a significant preference for the novel object ($p<0.001$) Cacna1c-Hypo mice did not ($p=0.757$; genotype x object interaction $p<0.05$). Cacna1c-Hypo mice showed significant hypometabolism in the hippocampus (dorsal subiculum $p<0.001$; CA1 $p<0.01$), perirhinal cortex ($p<0.001$), the prefrontal cortex (medial prelimbic $p<0.05$; infralimbic $p<0.01$), thalamus (mediodorsal, $p<0.01$; reticular $p<0.001$) and basal ganglia (striatum $p<0.01$; substantia nigra $p<0.01$). By contrast, cerebral metabolism was not altered in the amygdala of Cacna1c-Hypo mice. Conclusions: The induction of Cacna1c hypofunction in ketamine-activated brain networks impairs memory consolidation, as demonstrated by the ability of Cacna1c-Hypo mice to recognise a novel object at 1 hour but not 24 hours after acquisition. In addition, Cacna1c hypofunction in ketamine-activated brain networks induces hypometabolism in neural subsystems implicated in memory acquisition and consolidation. Financial Support: This work was supported by Lancaster University.

D03

CEREBROVASCULAR CHANGES IN A MOUSE MODEL OF ALZHEIMER'S DISEASE FOLLOWING LIPOPOLYSACCHARIDE (LPS) TREATMENT.

Culi N, School of Life Sciences, University of Nottingham, The University of Nottingham Medical School Queen's Medical Centre Nottingham UK, NG7 2UH mbync@nottingham.ac.uk

Agostini A(1), Serres S(1), Pardon MC(1)

(1) As presenting author

Inflammation is regarded as a key contributor in the pathogenesis of Alzheimer's disease (AD) with altered proinflammatory marker profiles associated with cognitive decline. Vascular inflammation could cause structural changes to cerebral vessels. This may disrupt blood brain barrier (BBB) function which plays an important role in amyloid beta (Aβ) clearance, and as such increase parenchymal Aβ plaque load and associated cognitive dysfunction. The aim of this project is to determine whether structural changes occur within the cerebrovasculature when inflammation is induced in a mouse model of AD. Lipopolysaccharide (LPS, 100ug/kg i.v.), a toll-like receptor 4 agonist, was used to induce inflammation via systemic infection in APPswe/PS1de9 mice and their wildtype littermates (n=4 per sex and genotype). Mice were challenged twice, 2 weeks apart, to allow consideration for cerebrovasculature changes with tolerance towards LPS. This thereby yields three treatment conditions: LPS/LPS, PBS/LPS and a PBS/PBS group to serve as a vehicle control. Anti-collagen IV immunostaining was carried out for the assessment of cerebral vessel diameter changes with LPS treatment in the cortex and hippocampus. Preliminary assessment on one cortical region of interest (0.25mm2) in one image per animal shows no significant changes with sex ($F(1,18)=0.44$), $P=0.51$), genotype ($F(1,18)=0.04$, $P=0.83$) and treatment ($F(2,18)=0.68$, $P=0.52$) or interaction between these factors. This data suggests that there is no significant damage to cerebral vessels at 7 days post infection.

However we will also verify in vivo whether subtle changes in BBB integrity occurs with LPS treatment, using magnetic resonance imaging (MRI). T2 weighted MRI will be used to detect oedema associated with inflammation, whilst gadolinium enhanced T1 weighted MRI will be used to observe BBB permeability detecting any points of BBB breakdown. Funding Acknowledgements: BAP in vivo training award. UoN Vice Chancellor scholarship to AA.

D04

THE WISTAR KYOTO RAT DISPLAYS A NUMBER OF COGNITIVE DEFICITS, SOME OF WHICH ARE SEX-SPECIFIC

Doherty H, Dept of Pharmacology and Therapeutics, NUI Galway, University Rd, Galway, 0000 h.doherty1@nuigalway.ie

Kelly JK(1)

(1) As presenting author

There is a growing awareness of examining both sexes in pre-clinical research, rather than just male subjects. With regard to the Wistar Kyoto rat (WKY), we have found that sex differences exist in its anxiety- and depressive-like phenotype, with only male WKY subjects exhibiting novelty induced hypophagia and anhedonia compared to SD counterparts (Burke, N., et al 2016, Physiology and Behaviour, 167, 28-34). The aim of the current study was to extend this work by investigating if cognitive deficits exist in the WKY model, and if so whether there are any sex differences. We chose the novel object recognition (NOR) test to examine contextual memory, the 3 chamber sociability test for social recognition and the Morris water maze (MWM) for spatial memory. Male and female Sprague-Dawley (SD) and WKY rats were 7 weeks old on arrival. After a 4 week acclimatisation period, animals were divided into two subsets (8 per group) for examination of either the 3 chamber sociability test or NOR test, whilst the subsequent MWM test was evaluated on an equal number of animals drawn from each subset. Data were analysed by 2-way ANOVA followed by SNK post hoc tests where appropriate; $p<0.05$ vs relevant strain groups. In the 3 chamber sociability test, male (but not female) WKY rats displayed a decreased preference for an unfamiliar rat in the sociability trial ($p<0.05$), but no differences in the subsequent social preference trial. In the NOR test, both male and female WKYs spent significantly less time interacting with the objects in the acquisition trial ($p<0.01$), with a trend for a reduced discrimination index (DI) in the WKY groups. In the MWM, male WKY rats displayed significantly longer latency times for the hidden platform during the acquisition trials, whilst in the probe trial both male and female WKY groups spent significantly less time in the target quadrant in the 1st minute of the trial ($p<0.01$). To conclude, the WKY model demonstrates a number of deficits in the cognitive tests examined, with greater effects observed with the male WKY subjects, a finding also observed in our previous examination of certain anxiety and depression related behaviours. Financial support for the work presented is from a postgraduate scholarship from the College of Medicine, Nursing and Health Sciences, NUI Galway.

D05

INVESTIGATION INTO EPISODIC MEMORY DEFICITS IN AN ANIMAL MODEL FOR SCHIZOPHRENIA.

Lambert SL, Division of Pharmacy & Optometry and School of Biology, University of Manchester (UoM), Stopford Building, Room 2.019a, Oxford Rd, Manchester, M13 9PT sarah.lambert-4@student.manchester.ac.uk

Neill JC(1), Gigg J(2)

(1) As presenting author; (2) Faculty of Biological Medical and Health Sciences, Room 3.800 Stopford Building, University of Manchester, Oxford Road, Manchester, M13 9PT

Introduction Deficits in memory for autobiographical events (episodic memory) in schizophrenia are largely treatment-resistant (Barch & Sheffield, 2014 World Psychiatry 13(3): 224-232). Establishing episodic memory deficits in a pre-clinical model is, important for improved drug discovery; however, this has only been demonstrated once to our knowledge, using the What-Where-Which (WWWhich) paradigm (Le Cozannet et al., 2010 Int J Neuropsychopharmacol. 13(8): 1011-1020). In this study we sought to control

for possible confounds in relation to preserved object memory by adopting a continuous version of the WWWhich task (cWWW; Ameen-Ali et al., 2012 J Neurosci Methods 211(1): 66-76). We have repeatedly shown that sub-chronic phencyclidine (scPCP) induces a robust deficit for object memory in a standard novel object recognition task while scPCP rats have intact object memory if tested in a continuous version of this task (cNOR), where they are not removed from the test arena between task phases (Grayson et al, 2014 Behav Brain Res. 266: 188-92). This suggests that NOR deficits are due to sensory disruption. It is possible, therefore, that the WWWhich deficit previously reported in the standard version of the WWWhich task was due to a more fundamental deficit in object memory. As these authors did not report whether object memory was intact in their animals, we investigated for the first time whether scPCP-treated animals demonstrate a deficit in a cWWW task for episodic-like memory. Methods Adult female Lister Hooded rats were administered vehicle (0.9% saline, i.p.) or PCP (2mg/kg, i.p.) twice daily for 7 days, followed by 7 days washout (n=10 per group). The NOR task was used to establish a cognitive deficit, followed by the cWWW and then cNOR, in both arenas. Exploration time and discrimination index data were analysed using ANOVA and student's t-test. Results We confirm that scPCP rats were impaired for NOR ($p<0.05$), but not cNOR, and provide new evidence of a robust deficit in the cWWW ($p<0.0001$). Conclusions This supports the conclusions that scPCP rats (a) show a NOR deficit due to distraction and (b) have a robust deficit for episodic-like memory when tested in a task that preserves short-term object memory. This task could provide a useful method for identifying novel therapeutic approaches for restoring episodic memory deficits of relevance to schizophrenia and other disorders. No external funding was involved in this study.

D06

OPENING THE FILE DRAWER ON FAILURES IN EXPERIMENTAL HABIT INDUCTION

Gillan CM, School of Psychology, Trinity College Dublin, Trinity College Institute for Neuroscience, Trinity College Dublin, Dublin 2, Ireland, Dublin 2 gillancl@tcd.ie

de Wit S(1), Kindt M(1), Knot S(1), Verhoeven AAC(1), Robbins TW(4), Gasull J(2), Evans M(3), Mirza H(3), Gillan CM(5)

(1) Department of Clinical Psychology, University of Amsterdam, The Netherlands; (2) Department of Neurochemistry and Neuropharmacology, CSIC-Institut d'Investigacions Biomèdiques de Barcelona, Barcelona, Spain; (3) Department of Psychology, New York University, New York, USA; (4) Department of Psychology, University of Cambridge, Cambridge, UK; (5) School of Psychology, Trinity College Dublin, Ireland

Introduction. Habits are repetitive behaviours that become ingrained with practice, routine and repetition. The more we repeat an action, the stronger our habits become. Behavioural neuroscientists and clinical psychologists have become increasingly interested in this topic because habits may contribute to aspects of maladaptive human behaviour, such as compulsive behaviour in psychiatry. Numerous studies have demonstrated that habits can be induced in otherwise healthy rats by simply over-training stimulus-response behaviours. However, despite growing interest in this topic and its application to psychiatry, a similar body of work in humans is absent. Only a single study has been published in humans that shows the effect on over-training on habit expression (Tricomi et al., European Journal of Neuroscience, 2009). Method. We carried out five separate experiments designed to replicate the finding that extended training of instrumental behaviour leads to the development of inflexible habits in healthy humans. We used four experimental paradigms, two versions of an instrumental avoidance task (Exp 1A & 1B; based on Gillan et al., Biological Psychiatry, 2014), one appetitive slips-of-action task (Exp 2; based on de Wit et al., Journal of Neuroscience, 2012) and another appetitive task that was previously used to show the effect in healthy humans (Exp 3A & 3B; based on Tricomi et al., European Journal of Neuroscience, 2009). The duration of training ranged from just a couple of minutes to 3 days of training and was manipulated across groups in 4 of these studies and within-group in 1 study. Behaviours that were trained minimally were compared to those that were trained extensively on the gold standard test for habits, 'outcome devaluation'. This procedure involves rapidly reducing the value of instrumental outcomes and testing if behaviour updates to reflect this change in value. If subjects continue to respond to familiar stimuli, regardless of the value of the outcome associated with that response, then behaviour is deemed a habit. Three hundred and four

subjects took part, and the smallest group size in any study was N=24. Data from the test phase of each test were analysed using repeated measures analysis of variance with training condition and outcome value as independent variables and number of responses executed (or response rate in Exp3A-b) as the dependent measure. Results. Extended training did not lead to greater habits than minimal training in any of our 5 investigations, using two versions of an avoidance learning task (Exp1A-B;), an appetitive slips-of-action task (Exp2), and the task used in the original demonstration (Exp3A-B). There were individual differences in devaluation sensitivity, as seen in prior studies, but critically this could not be experimentally manipulated via training duration. Conclusion. Habits are difficult to experimentally induce in health humans. Our findings are consistent with the view that current outcome-devaluation tasks tap predominantly into goal-directed control, rather than the gradual build-up of stimulus-response habits in healthy humans. Alternatively, training durations in these paradigms might be insufficient to instil sufficiently strong habits in humans in a laboratory setting. These data have implications for future research in healthy and disordered populations, where habits are thought to play an important role.
Funding: The research conducted in Amsterdam was supported with a VIDI grant from the Netherlands Organisation for Scientific Research (NWO) awarded to S de Wit (016.145.382). The research conducted at New York University was supported by a Sir Henry Wellcome Postdoctoral Fellowship (101521/Z/12/Z) awarded to C.M. Gillan. C.M Gillan is supported by MQ: transforming mental health (MQ16IP13). The research conducted at University of Cambridge was supported by a Wellcome Trust Grant (089589/Z/09/Z) awarded to TW Robbins, BJ Everitt, AC Roberts, JW Dalley and BJ Sahakian.

D07

EVALUATION OF A SHORT, ROBUST FMRI CONTROL TASK FOR PHARMACOLOGICAL FMRI STUDIES

Harvey-Cox JL, Division of Brain Sciences, Imperial College London, Burlington Danes Building, Imperial College London, Hammersmith Hospital, Du Cane Road, London, W12 0NN jessicaharveycox@gmail.com

Demetriou L(1), Wall MB(1)

(1) Imanova Limited, Burlington Danes Building, Imperial College London, Hammersmith Hospital, Du Cane Road, London, W12 0NN, UK

Introduction Functional magnetic resonance imaging (fMRI) is a popular method for examining pharmacological effects on the brain. However, the BOLD response is an indirect measure of neural activity, and as such is vulnerable to confounding effects of pharmacological probes (Bourke & Wall, 2015, Frontiers in Neuroscience, 9:167). Controlling for such non-specific effects in pharmacological fMRI studies is an important consideration. We have developed a short (5-minute) standardised control task, for use in pharmacological fMRI studies that is simple to administer, and yields a number of readouts. Methods In this study we present a novel fMRI protocol programmed in Psychopy (a free, open-source application) for use within pharmacological fMRI studies as a control task. The task consists of five functionally discreet three-second trial types, which are each repeated 20 times in a predetermined randomised order. The trial types are: visual (a drifting grating), auditory (six pure tones presented for 0.5s each, at randomly selected frequencies), motor (three button presses), cognitive, and null (baseline). In version one, the 'cognitive' condition consists of six eye-movements to random locations on the screen. In version two, the cognitive condition is a brief working memory task involving memorising short letter strings. The task's performance was examined in a group of 15 subjects, using a 3-Tesla Siemens Magnetom Trio scanner, and a standard EPI sequence (TR=2, TE=31, 36 slices, 3mm isotropic voxels). Analysis was completed with FSL using standard parameters (head-motion correction, 100s temporal filtering, 6mm spatial smoothing, coregistration to a standard template, modelling with a general linear model) and statistical thresholds ($Z=2.3$, $p<0.05$, cluster-corrected). Results The task performed as expected. Visual and auditory trials produce strong and selective activation in occipital lobe and temporal lobe, respectively. Motor trials produce activation in contralateral motor cortex, ipsilateral cerebellum, and the striatum. In version one, the cognitive condition produced clear activity in the frontal eye-fields (and visual cortex). In version two, the cognitive condition produced results consistent with working memory tasks (e.g. the N-back), including the intra-parietal sulcus, dorsolateral prefrontal cortex, and anterior cingulate. Conclusions This demonstration of a brief, robust fMRI protocol will be valuable for researchers conducting pharmacological fMRI studies, and others who require a simple test program (e.g. for comparing different

MRI acquisition sequences). We are making the stimulus code and analysis templates for this task freely available on https://figshare.com/, and we encourage interested researchers to download and examine the program. Financial Sponsorship- Imanova ltd.

D08

COGNITIVE BIAS MODIFICATION OF FACE EMOTION PERCEPTION: A RANDOMISED CONTROLLED TRIAL OF TRANSFERENCE TO COGNITIVE AND SELF-REPORT MEASURES IN HEALTHY VOLUNTEERS

Peters SE, Institute of Cognitive Neuroscience, UCL, Alexandra House 17 Queen Square Bloomsbury, London, WC1N 3AR selizabethpeters@gmail.com

Lumsden J(3), Peh OH(1), Penton-Voak IS(2), Munafò MR(2), Robinson OJ(1)

(1) As presenting author; (2) School of Experimental Psychology, University of Bristol, Clifton BS8 1TU; (3) School of Experimental Psychology, University of Bristol, Clifton BS8 1UB

Introduction: Cognitive bias modification (CBM) has shown some promise as a potential low-intensity intervention for mood disorders, but findings are mixed and in some cases suffer from experimental limitations (e.g., insufficient bias modification). Method: The current study explored whether a CBM task designed to shift emotional perception of faces would transfer to: a) a battery of affective cognitive tasks, and b) self-reported mood disorder symptoms. We conducted a preregistered, double-blind randomised controlled trial in 104 healthy participants, who either received eight online sessions of CBM (N=52) or eight sessions of sham CBM (N=52) across one week. Results: Frequentist and Bayesian analyses were carried out. While CBM successfully induced a substantial positivity bias in interpretation of ambiguous facial expression in the intervention group ($F(7,308)=9.811$, $p<0.001$, $BF10=1.739*1025$), this failed to transfer to the majority of cognitive tasks or mood symptoms (all $p>0.05$, $BF<1.081$). However, there was weak, inconclusive evidence of transfer effects for a self-report measure of stress response ($F(1,101)=4.999$, $p=0.028$, $BF10=1.081$) and a cognitive measure of anhedonia ($F(1,101)=3.655$, $p=0.059$, $BF10=0.433$). We also found some evidence of a ceiling effect, whereby transference effects were only evident in those with high levels of trait anxiety on a go/no-go task under threat of shock ($F(1,48=7.322$, $p=0.009$) and a dot-probe task ($F(1,48)=4.198$, $p=0.046$). Conclusion: Whilst we see clear evidence of bias modification in the intervention group, transfer effects to symptoms and other cognitive tasks were weak and inconclusive. Further work is needed in both larger and clinical samples, however we sound caution that CBM training effects may not transfer to other cognitive or symptom domains. This research was funded by a Medical Research Council Career Development Award to OJR (MR/K024280/1) and a Medical Research Foundation Equipment Competition Grant (C0497, Principal Investigator OJR).

D09

DISSECTING CONTRIBUTIONS TO ANHEDONIA FROM MOTIVATION TO EXERT PHYSICAL EFFORT FOR REWARDS: A COMPUTATIONAL ANALYSIS OF BEHAVIOUR

Valton V, Institute of Cognitive Neuroscience, University College London, Institute of Cognitive Neuroscience, 17 Queen square, Alexandra House,, WC1N 3AZ vincent.valton@ucl.ac.uk

Gray A(1), VanUrk S(1), Payne MEM(1), Roiser JP(1)

(1) As presenting author

Motivation can be defined as the willingness to exert effort in order to attain a preferred outcome (Niv et al. 2007,Psychopharmacology,191,507–520), which is strongly dependent on the magnitude of anticipated reward and required effort (Walton et al. 2006,Neural networks,19,1302-1314). Motivation to obtain rewards is an important cognitive component of anhedonia; a symptom that has profound effects on everyday function in several psychiatric disorders, especially depression (Treadway et al. 2009,PLoS One,4,8). However, the precise cognitive processes that are associated with depressive and anhedonic symptoms are unclear. We tested 103 healthy subjects on a physical effort task, the Apple Gathering Task (Bonnelle et al. 2015,Journal of Physiology,109,16-26). Twelve subjects were excluded due to incomplete data or inconsistent calibration results. Subjects were required to squeeze a hand dynamometer to win points, with the strength required for success calibrated to their own ability to generate force. Effort

was manipulated by adjusting the strength required on a given trial, while reward was manipulated by adjusting the amount of points that could be gained. On each trial, subjects could either accept an offer and exert the effort, or refuse and move onto the next trial. We analysed participants' choices to exert effort using 70 different computational models of trial-by-trial behaviour. The winning model from model comparison allowed us to extract parameters reflecting individual levels of reward and effort sensitivity. We then correlated these parameters with questionnaire measures of anhedonia, depression and anxiety (Chapman Physical Anhedonia Scale – CPAS, Dysfunctional Attitude Scale – DAS, and the State Trait Anxiety Inventory – STAI). There was a significant interaction between effort level and reward magnitude on the probability of accepting an offer ($F(5.14,458.24)=20.08$, $p<0.001$). The probability of accepting an offer also decreased significantly with increasing effort level ($F(1.813,161.34)=185.22$, $p<0.001$), and increased significantly with increasing reward level ($F(1.812,161.23)=107.73$, $p<0.001$). Computational analysis (using the winning model) revealed that subjects with higher effort sensitivity parameters scored higher on anhedonia (CPAS: $r=-0.21$, $p=0.04$) and dysfunctional attitudes (DAS: $r=-0.22$, $p=0.03$), while those with lower reward sensitivity scored higher on trait anxiety (STAI Trait: $r=-0.35$, $p=6.7e-4$). Similar findings emerged when the parameters were correlated with low-mood, anhedonia and negative cognitive bias latent variables extracted using factor analysis. Using computational modelling allowed us to dissect the individual contributions of reward and effort on motivation. These tools may provide a better understanding of the underlying mechanisms of anhedonia in psychiatric populations. This project was funded by the Wellcome Trust.

D10

REWARDS AND PUNISHMENTS DIFFERENTLY AFFECT MOTIVATION TO EXERT COGNITIVE EFFORT

Mkrtchian A, ICN, UCL, 17 Queen Square, London, WC1N 3AR a.mkrtchian@ucl.ac.uk

Valton V(1), Roiser JP(1)

(1) ICN UCL, 17 Queen Square, London, WC1N 3AR

Introduction: Motivation involves cost-benefit valuations between the willingness to exert effort and the desired outcome. The desired outcome is often defined as a potential reward, however we can also be motivated to exert effort to avoid punishment. How motivation differs between effort-related decisions involving potential rewards and potential losses is unknown. Here we aimed to characterise motivation to avoid punishment compared with motivation to obtain rewards in a paradigm measuring willingness to exert cognitive effort. Methods: Participants were presented with offers to perform a challenge (categorise 10 odd/even digits under time pressure) of a certain effort level to either win money or to avoid losing money. Effort levels (20, 50, 80%) were manipulated by varying the challenge trial time and were calibrated to each individual. Participants performed two separate versions of the cognitive effort decision-making task. In one version, offers were presented to exert cognitive effort to obtain rewards (3, 6, 9 points; N=50) and in the other, participants were given offers to exert cognitive effort to avoid punishments (-3, -6, -9 points; N=49). The tasks were administered in a counterbalanced order and tested over two sessions to assess reliability (mean test-retest interval = 13.96 days). Reliability of responses was measured with intra-class correlation coefficient (ICC). Results: As expected, a repeated measures ANOVA revealed a significant interaction between effort levels and reward magnitude, indicating that the probability to accept an offer decreased with increasing effort levels and increased with increasing reward levels in the first ($F(2.34,114.51)=13.08$, $p<0.001$) and second session ($F(2.07,101.60)=9.60$, $p<0.001$). The same pattern was observed for decisions involving potential losses. Offer acceptance rates decreased with increasing effort and increased with increasing punishment levels over both sessions (session 1: $F(2.18,104.439)=10.09$, $p<0.001$; session 2: $F(1.88,90.11)=12.42$, $p<0.001$). Interestingly, the probability to accept an offer was less sensitive to changes in punishment magnitude, remaining high regardless of the punishment level, compared with changes in rewards (session 1: $t(48)=3.03$, $p=0.024$; session 2: $t(48)=4.54$, $p<0.001$). This difference in reward and punishment sensitivity was highly reliable (ICC=0.77). Conclusions: We show for the first time that rewards and punishments affect motivation to exert cognitive effort in different ways, and that this difference is stable over time. This provides a greater understanding of the processes underlying motivated behaviour, which is important, as motivation is a central cognitive

component of many psychiatric disorders. Funding: This study was funded by the Wellcome Trust–NIH PhD Studentship Programme.

D11

A CAUSAL ROLE FOR NORADRENALINE IN CONTROLLING THE INFLUENCE OF PRIOR BELIEFS DURING DECISION MAKING: A DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

Lawson RP, Wellcome Trust Centre for Neuroimaging, University College London, 12 Queen Square, WC1N 3BG rebecca.lawson@ucl.ac.uk

Bisby J(1), Imber S(1), Burgess N(1), Rees G(1)

(1) Institute of Cognitive Neuroscience, University College London, WC1N 3AR

Providing a neurocomputational account of how 'top-down' prior expectations are balanced against 'bottom-up' sensory reality is one of the core aims of the computational psychiatry endeavour; as this mechanism may be vulnerable in many psychopathologies (e.g. psychosis, autism). In a state where one's beliefs are uncertain (e.g. in volatile conditions), prior expectations should be suppressed (Yu & Dayan, Neuron, 46, 681–692). Noradrenaline (NA) is hypothesised to play a key role in signalling volatility, and so its blockade should enhance the influence of prior expectations on behaviour, increasing the effects of encountering unexpected stimuli. In order to test this hypothesis, we investigated the effects of attenuating noradrenergic neurotransmission during probabilistic associative learning. Behavioural effects of the non-selective β-adrenergic receptor antagonist Propranolol (40mg) were probed using a between-subjects, double-blind, placebo-controlled design. Healthy volunteers (n=21, Propranolol, n=19, Placebo) performed binary classification of images as either faces or houses, and images had either high or low visual noise added. A tone preceding each image was either highly or weakly predictive of a given outcome, and these tone-image associations changed across time. A hierarchical learning model fit to participant behaviour allowed us to formally quantify 'surprise' (prediction errors) about cue-outcome contingencies and changes in these associations over time (volatility). Concurrent pupillometry provided a biomarker of phasic noradrenergic responses. We observed a significant three-way interaction between expectation, visual noise and drug ($P<0.02$). Under placebo conditions, reaction times were slower for unexpected, relative to expected, stimuli when visual noise was high ($P<0.001$). As predicted, this indicates that prior expectations exert a greater influence on behaviour when sensory inputs are less certain. Crucially, this effect was enhanced following NA antagonism (i.e. greater RT difference, $P<0.02$), suggesting that NA blockade can augment the influence of prior beliefs during perceptual decision making. Computational-pupillometry analyses indicate that, while pupil dilation increases with increasing volatility (e.g. when the tone-face/house association changes), this is reduced under Propranolol (cluster-based permutation approach at 2000 permutations (FWE alpha=0.05, 2-tailed), implicating the integrity of NA signalling in the representation of volatility. These findings provide direct evidence for noradrenaline's role in shifting the balance between prior beliefs and sensory inputs by signalling the changeability of the environment, and provide a framework for investigation of various psychopathologies in which the problems integrating expectations with reality is hypothesised. This study was supported by the Wellcome Trust.

D12

THE LONG TERM EFFECTS OF MDMA ON EMPATHY: DOES MDMA ENHANCE FEELINGS OF EMOTIONAL EMPATHY?

Kosmider S, Psychology, University of Exeter, Washington Singer, Perry Rd, Exeter, EX4 4QG s.kosmider@hotmail.com

MDMA has been shown to enhance feelings of emotional empathy and prosocial behaviour (Hysek et al. 2014, Journal of Social cognitive and affective neuroscience, 11, 1645–1652). Empathy is associated with the development of a positive therapeutic alliance, associated with positive patient outcomes (Chabrol & Oehen, 2013, Journal of Psychopharmacology, volume 27 (9), pg. 865-866). Previous research has suggested that MDMA used in conjunction with Psychotherapy may be useful in treating patients suffering from anxiety disorders like treatment resistant Post Traumatic Stress Disorder (PTSD), where patients often struggle to engage in the therapeutic alliance (Chabrol & Oehen, 2013). The relationship between

acute MDMA use and empathy has been examined, this research project aims to understand whether these effects can be found in chronic MDMA users. Seventy-nine drinkers and/or drug users above the age of 18 were recruited using flyers. Participants were assessed on empathy using the Interpersonal Reactivity Index (IRI, Davis, 1980, JSAS Catalog of Selected Documents in Psychology, 10, 85) and the Multifaceted Empathy Task (MET)(Dziobek et al. 2006, Psychiatry Research, 149, 321–324). This study used a single blind, between subjects design. Participants were divided into three groups (alcohol and no other drugs, polydrug MDMA - consumed MDMA at least ten times, and polydrug non MDMA). A 1 way factorial ANCOVA was conducted. The effect of MDMA use on empathy when controlling for mood was examined (Positive and Negative Affect Scale, PANAS, Watson et al. 1988, Journal of Personality and Social Psychology, 54(6), 1063–1070). It was predicted that MDMA users would score higher in emotional empathy than non MDMA users. MDMA users scored higher in emotional empathy than non MDMA polydrug users ($P<0.05$), but not higher than the alcohol condition ($P>0.05$). Further analysis showed that MDMA users scored significantly higher in empathic concern (component of emotional empathy, IRI) than both conditions ($P<0.05$). This research suggests that chronic MDMA use might be associated with a component of emotional empathy, empathic concern. This could have practical implications for MDMA as an effective therapeutic tool, however, has reduced generalisability due to the limitations of a questionnaire. Future research should examine whether chronic MDMA use is associated with empathic concern using measures closer to real life social interactions. No sponsorship received.

D13

MDMA INCREASES ACTIVITY OF SOCIAL BRAIN AREAS AND COOPERATIVE RESPONSES WHEN INTERACTING WITH TRUSTWORTHY PLAYERS DURING AN ITERATED PRISONER'S DILEMMA

Gabay AS, Dept of Neuroimaging, IoPPN, KCL, De Crespigny Park (089) London, Se5 8AF anthony.a.gabay@kcl.ac.uk

Kempton MJ(1), Mehta MA(1)

(1) As presenting author

Introduction: Social decision-making is an increasingly popular field of study when investigating social cognitive deficits in psychiatric illness. The Prisoner's Dilemma (PD) is a social decision-making task which models cooperative behaviour and trust during interpersonal interactions. However, the psychopharmacology of the mechanisms underlying behaviour in this task is poorly characterised. In order to address this knowledge gap, we carried out a neuroimaging study with healthy participants to investigate the effect of the potent serotonergic compound, 3,4-methylenedioxymethamphetamine (MDMA), during an iterated PD. Methods: We administered 100mg MDMA or placebo to 20, male participants in a double-blind, placebo-controlled, crossover study design, prior to playing an iterated PD during fMRI scanning. Participants played repeated rounds with trustworthy and untrustworthy opponents, who differed in how much they cooperated. Participants also played non-social, control opponents. On each round participants chose whether to compete or cooperate, received feedback of the other player's decision, and were asked rate their trust in the other player. Results were analysed using repeated-measures logistic regression, implemented with generalized estimating equations. Results: Participants behaved more cooperatively with trustworthy, but not untrustworthy, opponents during the MDMA session compared to the placebo session (respectively: OR = 2.01 95% CI 1.42 – 2.84, $p < 0.001$; OR = 1.37 95% CI 0.78 – 2.30). This was accompanied, when receiving feedback during the trustworthy condition, with increased activation of the right posterior superior temporal sulcus, bilateral central operculum/posterior insula, and mid-cingulate cortex (FWE-corrected $p < 0.05$). There were no changes in trust ratings for any opponent across experimental sessions. Conclusion: MDMA caused an increase in cooperative behaviour in the PD, but only for trustworthy opponents. Underlying this was a change in brain activity of regions often linked to social cognition, during feedback of cooperative players' decisions. Previous evidence suggests that these changes may represent alterations in the engagement with, and appraisal of, other players' behaviour. Overall, our findings highlight the context-specific nature of serotonergic mechanism underlying social decision-making. This work was supported by the MRC-IoPPN Excellence PhD studentship scheme.

D14

UNDERSTANDING COGNITIVE FUNCTIONS RELATED TO DRIVING FOLLOWING KAVA (PIPER METHYSTICUM) USE AT TRADITIONAL CONSUMPTION VOLUMES

Aporosa A, Traffic and Road Safety Research Group (School of Psychology) / Anthropology Programme, The University of Waikato, FASS (University of Waikato) Private Bag 3105 Hamilton New Zealand, 3240 apo.aporosa@waikato.ac.nz

Introduction: Kava (Piper methysticum), a traditional and culturally significant Pacific Island beverage, produces soporific relaxant effects similar to Benzodiazepine (Sarris et al, 2012, Journal of Human Psychopharmacology Clinical and Experimental, 27:262-9). Traditional users consume this drink at volumes 32 times greater than pharmacologically recommended doses (Aporosa et al, 2014, Anthropologica, 56:163-75), with reports suggesting 70% of users frequently drive following kava use (Maneze et al, 2008, Australian & New Zealand Journal Of Public Health, 32:314-6). Prompted by concerns regarding driver impairment post kava use, this seminal research investigated the effects of kava on two cognitive functions related to driving. Research was based on a traditionally influenced kava session. Methods: Kava consumers (n=20 [18 male/2 females], mean age = 35.35) attended a six hour kava session, each drinking an average 3.52 litres (SD = 0.713 litres) of kava. Also present were a non-kava consuming control group (n=20 [18 male/2 females], mean age = 35.1). At baseline all participants completed computerised tests (Vienna Test System: Traffic WAFA Alertness and WAFG Divided Attention) to assess reaction time, perception and attention. Re-testing was conducted hourly over the six hour period. Pre/post analysis was conducted comparing within person and between group change. Statistical modelling is based on ANOVA and independent t-tests. Results: Data analysis indicated no statistically significant ($p<0.05$) difference between reaction time [$F=(13,264)$, 0.582, $p=0.868$] and divided attention [$F=(13,264)$, 0.834, $p=0.624$] both within person and between groups at any measurement point over the six hour testing period. Mean reaction time and divided attention at baseline was 249.95msec (SD=37.57) and 583.58msec (SD=226k .62) respectively. The control and active group mean reaction times at the final test were 256.70msec (SD=36.86) and 271.8msec (SD=46.32) respectively. The mean divided attention times for the control and active groups at the final test were 499.75msec (SD=167.62) and 568.32msec (SD=217.71). Conclusions: Kava at traditional consumption volumes was not correlated to response latency or impairment on perception and attention tasks. Further research beyond the assessment of these two cognitive functions is required to better understand if kava has any effect on driver ability. Sponsorship: The study is funded by the New Zealand Health Research Council (16/462) and the test battery was generously donated by Vienna Tests Systems, Germany.

D15

IS IMPAIRED RESPONSE CONTROL WHILST DRINKING ALCOHOL DUE TO IMPAIRED ATTENTION?

Stevens T, School of Psychology, University of Exeter, Washington Singer Laboratories Perry Road, EX4 4QG t.stevens@ex.ac.uk

Morgan CJA(1), McAndrew A(1), Carlyle M(1)

(1) School of Psychology, University of Exeter, Exeter EX4 4QG

Introduction: Previous work has shown that acute exposure to alcohol leads to impaired performance on response inhibition paradigms. This effect has been used as evidence for theories of impaired self-control following alcohol use (Fillmore et al., 2009). Performance in response inhibition paradigms is typically attributed to inhibitory control. However these findings might also be attributable to an impaired sensory detection process (Verbruggen et al., 2014). In this study we examined whether impaired stopping performance in inhibition paradigms due to alcohol intoxication (as compared to placebo) could be driven by changes in attentional control, which might affect our ability to detect stop signals. Method: 40 Participants were randomised to either receive alcohol (0.62 g/kg dose) or a placebo (similar strong sweet drink). They were given the alcohol / placebo dose and then 30 minutes later they performed the adapted stop signal task. This task asked them to respond quickly to a simple classification task or withhold their response when a visual ‘stop’ signal was presented. This stop signal could occur in the center of the screen near the classification task or further away from the task. On half of the trials, perceptual distractors (letter

strings) were presented surrounding the classification task. In a follow-up experiment, we replaced the letter strings with images with a neutral or an alcohol content to test whether the content of the distraction had a differential effect on stopping whilst drinking versus placebo. Results: The results were analysed using a 2 by 2 by 2 mixed ANOVA (experimental group, the location of the stop signal and the presence or absence of visual distractors) with stop signal reaction time as the primary dependent variable. Alcohol reliably impaired stopping in all conditions compared to placebo ($p=.01$). As in the previous studies distraction impaired stopping ($p<0.001$) but this effect of distraction did however not differ between alcohol and placebo. Distraction also impaired stopping in the follow-up experiment but as in the first experiment, this effect did not differ between alcohol conditions and the content of the distractors did not have a differential effect. Conclusions: These results suggest that effects of alcohol on response inhibition paradigms are primarily driven by a deregulation of motor control as opposed to increased problems detecting the stop signal. They also suggest that alcohol-related content in the visual environment does not further reduce subjects' ability to stop. Funded by the University Of Exeter.

D16

THE EFFECTS OF DELTA-9-TETRAHYDROCANNABINOL (THC) ON HIPPOCAMPAL MEMORY FUNCTION: A SYSTEMIC REVIEW

Petrilli K, UCL, Alexandra House, 17-19 Queen Square, Bloomsbury, London, Reino Unido, WC1N 3AR k.petrilli.16@ucl.ac.uk

Lees R(2), Hindocha C(5), Howes O(4), Curran V(5), Freeman T(1), Bloomfield M(3)

(1) Addiction Department, IoPPN, 4 Windsor Walk, Denmark Hill, London, SE5 8BB; (2) As presenting author; (3) Division of Psychiatry, UCL, Maple House, 149 Tottenham Court Road, London, W1T 7BN; (4) MRC London Institute of Medical Sciences, Psychiatric Imaging, Hammersmith Hospital Campus, Du Cane Road, London, W12 0NN; (5) Research Department of Clinical, Educational and Health Psychology, University College London WC1E 7HB

Introduction Cannabis is one of the most commonly used recreational drugs in the world with around 147 million users in 2016. Heavy cannabis use is associated with educational and occupational under-achievement and the main psychoactive ingredient of cannabis, Δ-9-Tetrahydrocannabinol (THC), is associated with memory impairment. Given the role of the hippocampus in memory function and the importance to public health of understanding the mechanisms by which cannabis use may affect cognition, we therefore sought to review the literature on the effects of THC on hippocampal memory function. Methods We conducted a systematic review by searching the terms "tetrahydrocannabinol" OR "THC" and "hippocampus" and "memory" Pubmed and Web of Science using PRISMA guidelines. Pre-clinical and clinical studies using THC, endocannabinoid CB1 receptor agonists or cannabis chronically and acutely were included. The studies were considered according to the age of THC consumption and to whether the focus of the study was on hippocampal functioning only or its functioning and memory performance. Results Hippocampal memory functioning has mainly been investigated in animals, and the literature on humans is scarce. Two acute pre-clinical studies show reductions in CA1 neurons excitability and memory disruptions. Nine chronic THC studies showed administration in animals results in hippocampal reductions in glutamate and Gamma-Aminobutyric acid (GABA) functioning. It also results in N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors with immature structural conformations, and NMDA receptor down-regulation. Chronic THC administration also leads to reduced hippocampal spine density and neuroplasticity markers. These findings have been related to poor performance in memory tasks including the radial arm maze and the novel object recognition tests. Human studies have mainly investigated the effects of chronic cannabis use. Two studies have reported lower hippocampal volume, alterations in memory-related brain activation, and episodic memory impairments. Further studies will be added to this review. Conclusion There is converging evidence that chronic THC exposure reduces memory-related hippocampal function. Animal studies suggest that the harmful effects of THC on hippocampal memory are increased when exposed during critical periods, such as adolescence. The biological mechanism behind this effect are not well understood, and it is necessary to investigate the translatability of this research to humans. This could help elucidate the correlation between THC and hippocampal memory deficits and clarify whether a causal effect is

present. Furthermore, clinical research is necessary to translate scientific discoveries into protective policy changes that could prevent cognitive impairment, and underachievement linked to heavy cannabis use. No sponsorship was received for this study.

D17

ACTION AND BELIEF UPDATE IN AN UNSTABLE ENVIRONMENT IN OBSESSIVE-COMPULSIVE DISORDER

Vaghi MM, Psychology, University of Cambridge, Downing St., Cambridge, CB2 3EB UK mmsv2@cam.ac.uk

Luyckx F(3), Sule A(2), Fineberg NA(4), Robbins TW(1), De Martino B(5)

(1) As presenting author; (2) Cumbria Partnership NHS Foundation Trust, NHS, Penrith, Cumbria, UK ; (3) Department of Experimental Psychology, University of Oxford, Oxford, UK; (4) Hertfordshire Partnership University NHS Foundation Trust and University of Hertfordshire, Hertfordshire, UK; (5) Institute of Cognitive Neuroscience, University College of London, Alexandra House, 17-19 Queen Square, London WC1N 3AR

Introduction Adaptive weighing of new input is required for flexible action and confidence updating and consequential optimal functioning in a dynamic environment. Based on the ego-dystonic nature of Obsessive-Compulsive Disorder (OCD) where patients compulsively engage in actions even if they recognize them as disproportionate, we tested the hypothesis that action and confidence might be independently updated in this patient population. Methods: Twenty-four OCD patients and 25 matched controls were tested on a modified predictive-inference task (McGuire et al., 2014; Nassar et al., 2010). Participants were required to position on each trial a bucket on a circular ring to catch particles flying from the middle of it and, before seeing where the particle would land, report their degree of confidence in their prediction. The particle's location was usually stable and sampled from a Gaussian distribution with small variations determined by noise to introduce uncertainty. At random intervals, particle's location was resampled from a uniform distribution thus requiring the participant to form a new belief about the mean of the new generative Gaussian distribution. Results: OCD patients were able to integrate action-outcomes over time as indicated by their reported confidence. However, this did not translate at the behavioural level. Their choices were prominently driven by the outcomes of recent actions and seemingly disregarded those further back in the OCD individuals' experience as indicated by higher learning rate in patients than controls (t-test t34=-3.587, p=0.001). Linear regression analysis using the different parameters of a quasi-optimal Bayesian learner as predictors, showed a stronger influence of prediction error in OCD patients compared with controls in driving action-updating p=0.018. In OCD patients there was a weakened relationship between action control and metacognitive reports of confidence (, p=0.007) which was most prominent in more severely ill patients (r=-0.426, p=0.038). Discussion: These findings showed a demonstration of a mismatch between internal beliefs about the environment and action choice in OCD patients, suggestive of the ability of forming an internal, accurate, model of the environment but a prominent failure in using it to guide behavior. Supported by a Senior Senior Investigator Award to TWR 104631/Z/14/Z.

D18

DOES N-ACETYLCYSTEINE AFFECT MEASURES OF COMPULSIVITY IN AN EATING-DISORDER RISK GROUP?

Pike AC, Department of Psychiatry, University of Oxford, Warneford Hospital Warneford Lane Oxford, OX3 7JX alexandra.pike@psych.ox.ac.uk

Sharpley AL(1), Williams C(1), Park RJ(2), Cowen PJ(1)

(1) As presenting author; (2) Department of Psychiatry, University of Oxford

Introduction: N-acetyl cysteine (NAC) is a dietary supplement which increases brain glutathione levels, and has recently been shown to have potential treatment efficacy in compulsive disorders ranging across OCD, trichotillomania and gambling (Dean et al., 2011. Journal of Psychiatry and Neuroscience, 36(2):78). The eating disorder Anorexia Nervosa has prominent elements of compulsivity, considering the characteristic

cognitive inflexibility, together with compulsive exercising, body-checking, and weighing (Godier & Park, 2014. Frontiers in Psychology, 5:778). The aim of the present study was to assess whether NAC might produce anti-compulsivity effects in a group of participants at increased risk of eating disorders. Methods: We studied 23 participants who scored between 9 and 19 on the EAT-26, but who did not meet diagnostic criteria for any specific DSM-5 disorder. They received up to 2400mg NAC daily and matching placebo for 9 days each in a double-blind, random-order, cross-over design. Psychological tests focusing on measures of compulsivity and impulsivity were carried out on the last day of each treatment period, with some key variables of interest being perseverative errors in the Wisconsin Card Sort Task, switching cost in the Attention Switching Task and delay aversion in the Cambridge Gambling Task. Results: Using a repeated-measures MANOVA, we found no main effect of NAC (Roy's Largest Root=0.42, F (6, 217) = 1.19, p = 0.365), which was replicated in paired-samples t-tests for each task. Additionally, there was no difference in EAT-26 score (t (22) = 1.587, p = 0.131) or self-starvation score (t (22) = 0.258, p = 0.798)(Godier and Park 2015. Eating Behaviors 17:10-13) after NAC compared to placebo. Conclusions: We found no effect of NAC dosed over 9 days on measures of compulsivity and impulsivity in high EAT scorers. There are a number of possible explanations for this lack of effect including insufficient duration of treatment, or low baseline compulsivity in this particular high-risk group. It is also possible that although NAC might be effective in disorders that are marked by compulsivity, it does not work primarily through reducing compulsive behaviour. Financial sponsorship: This study was funded by the MRC and the Department of Psychiatry, University of Oxford.

E01

GABAA RECEPTOR AVAILABILITY IN PATIENTS WITH SCHIZOPHRENIA: A PET STUDY USING [11C]-RO15

Reis Marques T, Psychiatric Imaging Group, London Institute of Medical Sciences (LMS), Faculty of Medicine, Imperial College London, Du Cane Road, London, W12 0NN tiago.marques@kcl.ac.uk

Veronese M(1), Rabiner I(1), Turkheimer FE(1), Howes OD(1)

(1) Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, Kings College London

An increasing body of evidence, derived from genetic, post-mortem and clinical studies implicates a reduction in GABAergic neurotransmission as an important component in the pathophysiology of schizophrenia. The GABA-A receptors are formed by five subunits, but receptors containing the α5 subunit are preferentially expressed in the hippocampus and other limbic regions, regions known to be involved and of particular importance in this disorder. So far, only one study has used a tracer specific to this subunit, and although no differences were observed between patients and controls there was a positive correlation between GABA-A availability and negative symptoms. In this preliminary study, we have used [11C]-Ro15, a radiotracer specific to the GABA α5 subtype receptor, to assess the expression of GABA-A receptors in schizophrenia. Method: We compared GABA-A receptor availability in the brains of 6 patients with schizophrenia and 6 matched healthy controls, using [11C]-Ro15 positron emission tomography (PET). All patients were on antipsychotic medication. Patients were excluded if on medication known to affect GABA neurotransmission. We estimate the volumes of distribution (VT) of [11C]-Ro15 in different brain regions. Results: There were no significant differences in [11C]-Ro15 VT between patients with schizophrenia and controls in the hippocampus (p = 0.351), temporal cortex (p = 0.377) or amygdala (p = 0.179). However, there was a trend towards a reduction in the VT for the Cingulate Cortex (p = 0.052) as well as for the insular cortex (p = 0.064). There were no correlations between psychotic symptoms and [11C]-Ro15 VT for any of the brain regions assessed. Conclusions: There were no significant differences in GABA-A receptor availability between schizophrenia patients and healthy controls in brain regions known to be implicated in schizophrenia. These results support the only previous study assessing GABA α5 subunit in schizophrenia. The implications of these findings will be discussed. This study was funded by an MRC intra-mural grant. There are no financial conflicts to report.

E02

HIPPOCAMPAL, PFC AND DOPAMINE DYSFUNCTION IN FIRST EPISODE PSYCHOSIS PATIENTS

Pepper F, Psychosis Studies, IOPPN, PO63 Institute of Psychiatry, King's College London Denmark Hill London, SE5 8AF fiona.pepper@kcl.ac.uk

Kotoula V(1), Jauhar S(1), Howes O(1)

(1) As presenting author

INTRODUCTION: During working memory tasks in first episode psychosis (FEP) patients, there is hypofunction in the prefrontal cortex (PFC) (e.g. (Schneider et al/2007/Schizophr Res/89(1-3)/198-210)) and hippocampus (Heckers et al./1998/Nat Neurosci/1(4)/318-323). Another feature of FEP is elevated striatal dopamine (e.g. (Lindstrom et al./1999/Biol Psychiatry/46(5)/681-688)). Dorsolateral prefrontal cortex (DLPFC) dysfunction in patients has been related to negative symptoms (van Veelen et al/2010/Schizophr Res/123(1)/22-29). There have been mixed results of the normalisation of prefrontal cortex function with treatment (e.g Mendrek et al./2004/Br J Psychiatry/185/205-214). PROJECT AIM: Is greater hippocampal and PFC dysfunction (during N-Back task) associated with greater dopamine striatal function and negative symptoms? Secondly, is there a normalisation in PFC activation after treatment that is related to negative symptoms? METHODS •A prospective observational cohort design with a nested case-control comparison using MRI and PET •n = 78 recruited (first episode psychosis patient = 45; healthy controls = 33). • Ki for [18F] fluorodopa uptake, regional brain activation (blood oxygen level dependent response; N-Back), and Positive and Negative Syndrome Scale (PANSS) scores were measured. ROI RESULTS BOLD Differences between patients and controls (at baseline): There was more activation in the hippocampus (x=22, y=-34, z=10; p = 0.035) and whole striatum (thalamus; x=20, y=-30, z=12; p = 0.045) in healthy controls than patients when participants performed the 2-back task compared to the 1-back condition Hippocampus and striatal dopamine: There was more activation in the hippocampus ROI in healthy controls than patients during 2-Back compared to 1-Back condition when Ki values from the associative striatum (x=22, y=-34, z=10; z = 3.44; p = 0.046) and whole striatum (x=22, y=-34, z=10; z = 3.71; p = 0.046) were covariates PFC and negative PANSS scores: There was more activation in patients than controls in the PFC (middle frontal gyrus; x=-30, y=22, z=38; p = 0.044 FWE) and whole striatum ROI (thalamus; x=-4, y=-10, z=4; p = 0.09 FDR). Normalisation of PFC: There was a significant reduction in general and total PANSS scores associated with a reduction in activation in Parahippocapmus Gyrus from baseline. CONCLUSIONS: There was significantly less activation in the hippocampus (Ki) and PFC (PANSS) in patients compared to controls. After 4-6 weeks of treatment, there was a significant reduction in general and total PANSS scores associated with a reduction in activation from baseline, but not negative symptoms as hypothesised. This is consistent with the notion that frontostriatal and hippocampal interactions have a critical role in the etiology of schizophrenia. No sponsorship received.

E03

A TEST OF THE TRANS-DIAGNOSTIC DOPAMINE HYPOTHESIS OF PSYCHOSIS: A PET STUDY IN BIPOLAR AFFECTIVE DISORDER AND COMPARISON WITH SCHIZOPHRENIA

Jauhar S, Psychosis Studies, King's Colllege, PO65 Denmark Hill Campus Psychosis Studies, King's College, London Se5 8AF, SE5 8AF sameer.jauhar@kcl.ac.uk

Nour M(1), Veronese M(1), Rogdaki M(1), Turkheimer F(1), Bonoldi I(1), Azis M(1), McGuire PK(1), Howes OD(1)

(1) As presenting author

Introduction The dopamine hypothesis suggests that dopamine abnormalities underlie psychosis irrespective of diagnosis (Howes and Kapur, Howes OD, Kapur S. S., Schizophr Bull. 2009 ;35(3):549–62), suggesting dopamine dysregulation in bipolar affective disorder as well as schizophrenia, in line with the research domain criteria (RDOC) approach (Insel TR, et al. Am J Psychiatry. 2010;167(7):748–751). However, this has not been directly examined in people presenting with bipolar disorder with psychosis. Our objective was to determine whether dopamine synthesis capacity is elevated in bipolar disorder with psychosis, and how this compares to schizophrenia, and matched controls. Furthermore, we wished to examine whether dopamine synthesis capacity is associated with psychotic symptom severity,

irrespective of diagnostic class. Methods 60 people participated in the study (22 with bipolar psychosis, (19 antipsychotic naïve/free), 16 with schizophrenia (14 antipsychotic naïve/free) and 22 matched controls) received 18F-DOPA PET examining dopamine synthesis capacity. Standardized clinical measures including the Positive and Negative Syndrome Scale (PANSS), Young's Mania Rating Scale (YMRS), Montgomery-Asberg Depression Rating Scale (MADRS), and Global Assessment of Functioning (GAF) were administered Results There was a significant effect of diagnostic group on Kicer (F (2, 57)=6.8, p<0.01). Striatal dopamine synthesis capacity (Kicer) was significantly elevated in both bipolar (mean=13.18 x10-3 min-1 [SD 1.08 x10-3 min-1], p<0.05) and schizophrenia (12.94 x10-3 min-1 [SD 0.79 x10-3 min-], p<0.05) groups, compared to controls (12.16 x10-3min-1 [SD 0.92 x10-3 min-1]). There was no significant difference in dopamine synthesis capacity between bipolar and schizophrenia groups. Kicer was significantly positively correlated with positive psychotic symptom severity in the combined schizophrenia and bipolar sample (n=32, r=0.52, p<0.01). There was a significant association between Kicer and positive psychotic symptom severity in people with bipolar disorder experiencing a current psychotic episode (n=16, r=0.6, p<0.01), this remaining significant after adjusting for manic symptom severity. Conclusion Dopamine synthesis capacity is elevated in first episode psychotic bipolar disorder, compared to controls, and this elevation is similar to that seen in first episode schizophrenia. Dopamine synthesis capacity is associated with positive psychotic symptoms in people with first episode psychotic bipolar disorder annd first episode schizophrenia, irespective of diagnostic class. This work was funded by the Wellcome Trust and Medical Research Council, UK.

E04

FIRST EXPERIENCE OF MEASURING GLUTAMATE SYNTHESIS IN VIVO IN SCHIZOPHRENIA USING 13C-MAGNETIC RESONANCE SPECTROSCOPY (MRS)

Gregory CJ, Neuroscience and Psychiatry Unit, University of Manchester, G700 Stopford Building Oxford Rd Manchester, M13 9PT catherine.gregory@manchester.ac.uk

Anton A(1), Lanz B(11), Chen C(7), Zhao S(3), Simpson EJ(10), Katshu MZUH(8), Rathnaiah M(2), Smallman RP(1), Liddle PF(9), Conen S(1), MacDonald IA(6), Morris PG(12), Williams SR(4), Deakin JFW(5)

(1) As presenting author; (2) B09, Institute of Mental Health, Jubilee Campus, University of Nottingham, Nottingham NG7 2TU; (3) G543 Stopford Building, Oxford Rd, Manchester M13 9PT; (4) G546 Stopford Building, Oxford Rd, Manchester M13 9PT; (5) G907 Stopford Building, Oxford Rd, Manchester M13 9PT; (6) oom D12 The University of Nottingham Medical School, Queen's Medical Centre, Nottingham NG7 2UH; (7) Room 23 Sir Peter Mansfield Imaging Centre, University Park, Nottingham NG7 2RD; (8) Room B-08 Institute of Mental Health, Jubilee Campus, Wollaton Road, Nottingham NG8 1BB; (9) Room B25 Institute of Mental Health, Innovation Park, Triumph Road, Nottingham NG7 2TU; (10) Room D65a The University of Nottingham Medical School, Queen's Medical Centre, Nottingham NG7 2UH; (11) Room MR3 Sir Peter Mansfield Imaging Centre, University Park, Nottingham NG7 2RD; (12) Room MR38 Sir Peter Mansfield Imaging Centre, University Park, Nottingham NG7 2RD

Introduction Schizophrenia is a chronic mental illness affecting 1% of the population. Studies using proton magnetic resonance spectroscopy (1H MRS) have shown increased glutamate in the anterior cingulate cortex (ACC) of patients early in the illness. However the functional implications of these findings are uncertain in the absence of measures of glutamate synthesis and metabolism. We describe the first application of the emerging technique of 13C MRS to measure glutamate synthesis and turnover in schizophrenia. Methods Patient groups with recent onset schizophrenia and with chronic illness, and age and gender matched healthy controls are being recruited across two centres (target of n=30 in each group). [1-13C] glucose was manufactured and underwent extensive stability and sterility testing. Participants were scanned at either 3 Tesla or 7 Tesla. After fasting [1-13C] glucose was infused intravenously to maintain a blood glucose clamp at 10-11mmol/l over the 1 hour localized 13C MRS acquisition. This leads to incorporation of the 13C label into glutamate via the tricarboxylic acid (TCA) cycle, allowing detection of glutamate and glutamine labelled at the C4 position (GluC4 and GlnC4), and to a lesser extent the C3 and C2 positions. The time-activity curves are used to calculate the rates of TCA metabolism, glutamate synthesis and glutamate to glutamine cycling within the 125ml voxel incorporating the anterior cingulate cortex. Results In the first 9 participants scanned at 3 Tesla, repeated 13C MRS spectra showed the appearance of GluC4 within 20 minutes from the start of the infusion, while GlnC4 and the other carbon positions of

glutamate and glutamine appeared above the noise level at a later stage in some subjects, consistent with the delayed metabolic labelling of these positions. One participant had unusable data due to head motion. The remaining 8 participants showed a GluC4 peak height of up to 13 times the background noise for the 1 hour averaged spectra. Conclusions Study set up was challenging, with arbitrarily stringent manufacturing requirements and developing an affordable, acceptable method for stability and sterilisation procedures. It was necessary to develop and implement specific MRS sequences, as well as dedicated radio frequency pulse calibration for the 1H and 13C nuclei, providing compensation for the different coil loading between participants and related power deposition issues. The scan procedure has been well tolerated despite the need for fasting, two intravenous cannulas and over an hour and a half scanning time. Sources of financial sponsorship: Medical Research Council.

E05

AUDITORY VERBAL HALLUCINATIONS IN FIRST EPISODE PSYCHOSIS – AN FMRI SYMPTOM CAPTURE STUDY

Dunne TF, College of Medical and Dental Sciences, University of Birmingham, Birmingham Medical School Edgbaston Birmingham, B152TT tfd289@student.bham.ac.uk

Mallikarjun PK(2), Reniers R(1), Farmah B(5), Broome M(4), Oyebode F(2), Wood S(3), Upthegrove R(2)

(1) The University of Birmingham, UK.; (2) The University of Birmingham, UK. Birmingham and Solihull Mental Health NHS Foundation Trust.; (3) The University of Birmingham, UK. The University of Melbourne, Australia. ; (4) The University of Oxford, UK. Oxford Early Intervention in Psychosis Service.; (5) Worcester Health and Care NHS Trust

Introduction Neurobiological models of auditory verbal hallucination (AVH) have been advanced by symptom capture functional magnetic resonance imaging (fMRI), where participants self-report hallucinations during scanning. To date, regions implicated are those involved with language, memory and emotion. However, previous studies focus on chronic schizophrenia, thus are limited by factors such as medication use and illness duration. Studies also lack detailed phenomenological descriptions of AVHs. This study investigated the neural correlates of AVHs in patients with first episode psychosis (FEP) using symptom capture fMRI with a rich description of AVHs. We hypothesised that intrusive AVHs would be associated with dysfunctional salience network activity. Methods 16 FEP patients with frequent AVH completed four psychometrically validated tools to provide an objective measure of the nature of their AVHs. They then underwent fMRI symptom capture, utilising general linear models analysis to compare activity during AVH to the resting brain. Results Symptom capture of AVH was achieved in nine patients who reported intrusive, malevolent and uncontrollable AVHs. Significant activity in the right insula and superior temporal gyrus (cluster size 141mm3), and the left parahippocampal and lingual gyri (cluster size 121mm3), $p<0.05$ FDR corrected, were recorded during the experience of AVHs. Conclusions These results suggest salience network dysfunction (in the right insula) together with memory and language processing area activation in intrusive, malevolent AVHs in FEP. This finding concurs with others from chronic schizophrenia, suggesting these processes are intrinsic to psychosis itself and not related to length of illness or prolonged exposure to antipsychotic medication. Funding Many thanks are offered to the Caring Minds Charity and Aberrant Experiences and Beliefs Theme LES (University of Birmingham) for their financial support.

E06

MU- OPIOID RECEPTOR AVAILABILITY IN SCHIZOPHRENIA PATIENTS WITH NEGATIVE SYMPTOM: A POSITRON EMISSION TOMOGRAPHIC STUDY USING [11C]-CARFENTANIL

Ashok AH, Psychosis studies, Institute of Psychiatry, Psychology and Neurosciences, 16 De Crespigny Park, London, SE5 8AF abhishekh.ashok@kcl.ac.uk

Marques TR(3), Rabiner EA(2), Howes OD(1)

(1) As presenting author; (2) Department of Neuroimaging, Institute of Psychiatry, Psychology and Neuroscience, Kings College London, London, UK; Imanova Ltd, London, UK; (3) Psychiatric Imaging Group, MRC London Institute of Medical Sciences, Hammersmith Hospital, Imperial College London, London, UK

Introduction: Negative symptoms, conceptualised as constellation of symptoms such as blunted affect, poverty of speech, amotivation, anhedonia and associality, lead to poor functional outcome and there is no effective treatment. While a substantial number of studies have investigated the neurobiology of positive symptom in schizophrenia, the molecular mechanisms underlying negative symptoms have received little attention. Preclinical-studies indicate bidirectional regulation of dopaminergic neurotransmission and -opioid receptor (MOR) stimulation via direct and GABA mediated dis-inhibition. MOR knock out animal models demonstrate anhedonic behaviour. There is also considerable interest in developing opiod system modulating drugs for the treatment of schizophrenia. However, the MOR availability in schizophrenia has not been studied. Using a MOR specific ligand [11C]-carfentanil, we report the first in vivo assessment of MOR expression in patients with schizophrenia. Method: We compared MOR availability in brains of 15 schizophrenia patients with moderate negative symptom and on antipsychotic treatment and 15 age and sex matched healthy controls using 11C-carfentnil positron emission tomography (PET). Regional estimates of binding potential (BPND) of [11C]-carfentanil was estimated using simplified reference tissue model with occipital cortex as reference tissue. Results: There was no significant difference in [11C]-carfentanil BPND between schizophrenia patients and healthy controls [patients vs control (mean ± SD): p-value] in thalamus [2.03 ± 0.33 vs 2.2 ± 0.26, 0.1], striatum [1.8 ± 0.41 vs 1.91 ± 0.2, 0.4], frontal lobe [1 ± 0.25 vs 1.1 ± 0.22, 0.4], cortical [0.93 ± 0.22 vs 0.98±0.18, 0.45], cingulate cortex [1.22 ± 0.3 vs 1.24 ± 0.22, 0.8], Hippocampus [0.7 ± 0.1 vs 0.71 ± 0.15, 0.7], amygdala [1.7±0.25 vs 1.8 ±0.33,0.3], midbrain [0.8 ± 0.16 vs 0.8 ± 0.16, 0.9] and hypothalamus [1.9 ± 0.3 vs 1.9 ± 0.4, 0.7]. Conclusions: Schizophrenia patients with moderate negative symptom have normal MOR availability. The implication of this finding for understanding neurobiology of negative symptom and future drug development will be discussed. Funding: This study was funded by the Medical Research Council and King's College London. Funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

E07

A PLACEBO-CONTROLLED STUDY OF THE ACUTE EFFECTS OF CANNABIS ON PSYCHOTIC-LIKE SYMPTOMS IN ADOLESCENTS AND ADULTS

Mokrysz C, Clinical Psychopharmacology Unit, UCL, 1-19 Torrington Place, London, WC1E 7HB c.mokrysz@ucl.ac.uk

Shaban N(1), Freeman TP(1), Curran HV(1)

(1) As presenting author

Adolescent cannabis users have a higher incidence of substance use disorder than adult users, and may be at increased risk of psychotic disorder. However, the acute subjective and psychotic-like effects of cannabis in adolescents are yet to be investigated. In adults, cannabis administration acutely induces psychotic-like symptoms. Auditory-verbal hallucinations (AVH) are an important symptom of psychotic disorders, but previous work has been inconclusive as to whether cannabis acutely induces AVH. In the present study, we assessed subjective and psychotic-like effects, including AVH, in adolescents and adults following acute cannabis administration. Male adolescent (n=20;16-17 years-old) and adult (n=20;24-28 years-old) cannabis users received active or placebo cannabis, on two occasions, in a placebo-controlled double-blind cross-over design. After inhaling vaporized active or placebo cannabis, participants completed a psychotic-like symptoms questionnaire, and a task designed to elicit AVH. For this task, participants listened to a series of auditory stimuli comprising of 'random-noise only' or 'random-noise + speech' and responded as to whether speech was present or not. Generalised Estimating Equations assessed differences in the rates of AVH between age groups and within treatments. Throughout the sessions, participants also provided ratings for subjective intoxication, including for 'stoned'. Active cannabis increased ratings of 'stoned' in both groups, but the effect was greater in adults than in adolescents (p=.033). Active cannabis increased self-rated psychotic-like symptoms in both groups, though adults reported higher cognitive disorganization than adolescents (p=.009), and cannabis increased anhedonia in adults (p=.001) but not adolescents (p=.925). On placebo, 35% of adolescents and 15% of adults experienced AVH during the 'random-noise only' stimuli, compared to 55% of adolescents and 45% of adults on active cannabis. Relative to placebo, active cannabis increased likelihood of AVH (b=1.128, SE=0.433, OR=3.09, 95% CI: 1.32,7.22). No differences in likelihood of AVH were found between age groups, and age group did not interact with treatment.

Cannabis administration acutely increased subjective intoxication, self-rated psychotic-like symptoms, and occurrence of AVH. Contrary to our predictions however, adolescents were no more vulnerable to the subjective or psychotic-like effects of cannabis than adults. Instead, we found blunted subjective effects and self-rated psychotic-like symptoms in adolescents relative to adults, though there was no age difference in the likelihood of AVH. These findings suggest that adolescent cannabis users may not be at increased risk of acute effects of cannabis; however, blunted acute effects may contribute to heavier real-world consumption patterns. This study was funded by MRC Studentship to CM.

E08

SAFETY OF LURASIDONE IN ADOLESCENTS WITH SCHIZOPHRENIA: INTERIM ANALYSIS OF A 24-MONTH, OPEN-LABEL EXTENSION STUDY

Tocco M, Medical Affairs, Sunovion Pharmaceuticals Inc, 84 Waterford Drive, Marlborough, MA, 01752 paladinmed@gmail.com

Correll C(3), Arango C(2), Goldman R(1), Cucchiaro J(1), Deng L(1), Loebel A(1)

(1) As presenting author; (2) Universidad Complutense, CIBERSAM, Madrid, Spain; (3) Zucker Hillside Hospital, Glen Oaks, NY

Introduction: Few data are available from prospective studies that demonstrate the long-term safety of second-generation antipsychotics in adolescents with schizophrenia. Lurasidone has demonstrated efficacy in the treatment of schizophrenia in both adults and adolescents. The aim of the current open-label trial was to obtain data on the long-term safety of lurasidone in adolescents with schizophrenia. Methods: Patients aged 13-17 years old with a DSM-IV-TR diagnosis of schizophrenia who completed a 6-week, double-blind, placebo-controlled lurasidone treatment study were eligible for enrolment in an extension study of the safety and effectiveness of 24 months of open-label, flexible-dose treatment with lurasidone 18.5-74 mg/d. This analysis summarizes the safety results from an interim analysis of an ongoing 2 year study. Safety measures included frequency of treatment emergent adverse events; and changes from open-label baseline in mean weight and median metabolic parameters and prolactin (observed case analysis). Results: A total 180 patients entered the extension study (male, 57.8%; mean age, 15.6 years), of whom 38.3% discontinued prematurely. Reasons for study discontinuation consisted of withdrawal of consent (12.8%), adverse events (11.1%), lost to follow-up (4.4%), lack of efficacy (4.4%), and other reasons (5.6%). The mean daily dose of lurasidone during the open-label treatment period was 51.6 mg/d. Discontinuation due to adverse events occurred in 11.1% of patients; the 3 most frequent adverse events leading to study discontinuation were schizophrenia (3.9%), suicidal ideation (1.7%), and psychotic disorder (1.1%). In the placebo-to-lurasidone treatment group (N=57), the 5 most frequent adverse events were headache (24.6%), nausea (14.0%), increased weight (14.0%), anxiety (10.5%), and agitation (10.5%); and in the lurasidone-continuation group (N=123), the 5 most frequent adverse events were headache (16.3%), anxiety (11.4%), agitation (10.6%), schizophrenia (8.9%), and depression (8.1%). Small median changes at 12 months were noted for cholesterol (+0.7 mg/dL), triglycerides (+4.1 mg/dL), glucose (+0.6 mg/dL), and prolactin (males, +0.1 ng/mL; females, +0.5 ng/mL). Mean change in weight at 12 months was +5.7 kg (vs. an expected weight gain of +2.8 kg). Conclusion: Long-term treatment with lurasidone was associated with few effects on body weight, lipids, glucose, and prolactin in this interim analysis of 12 month data from an open-label 24-month study of adolescents with a diagnosis of schizophrenia. The safety profile was consistent with results from previous adult studies with lurasidone. Sponsored by Sunovion Pharmaceuticals Inc. ClinicalTrials.gov identifier: NCT01914393.

E09

EFFECTIVENESS OF LURASIDONE IN ADOLESCENTS WITH SCHIZOPHRENIA: INTERIM ANALYSIS OF A 24-MONTH, OPEN-LABEL EXTENSION STUDY

Tocco M, Medical Affairs, Sunovion Pharmaceuticals Inc., 84 Waterford Drive, Marlborough, MA, 01752 michael.tocco@sunovion.com

Arango C(2), Correll C(3), Goldman R(1), Cucchiaro J(1), Deng L(1), Loebel A(1),

(1) As presenting author; (2) Universidad Complutense, CIBERSAM, Madrid, Spain; (3) Zucker Hillside Hospital, Glen Oaks, NY

Introduction: Few data are available from prospective studies that demonstrate the long-term effectiveness of second-generation antipsychotics in adolescents with schizophrenia. The aim of the current open-label trial was to obtain preliminary data on the long-term effectiveness of lurasidone in adolescents with schizophrenia. Methods: Patients aged 13-17 years old with a DSM-IV-TR diagnosis of schizophrenia who completed a 6-week, double-blind, placebo-controlled lurasidone treatment study were eligible for enrolment in an extension study of the safety and effectiveness of 24 months of open-label, flexible-dose treatment with lurasidone 18.5-74 mg/day, with an initial dose of 37 mg/d for the first 7 days. This analysis summarizes the effectiveness results from an interim analysis of an ongoing 2 year study. Effectiveness measures included the Positive and Negative Syndrome Scale (PANSS) total and positive and negative subscale scores, and the Clinical Global Impression-Severity (CGI-S) score. An ANCOVA was performed on last observation carried forward data (LOCF) available at week 28. Results: A total of 180 patients entered the extension study, based on the current interim analysis (male, 57.8%; mean age, 15.6 years). The mean dose of lurasidone during the open-label treatment period was 51.6 mg/d. At the end of 6 weeks of double-blind treatment, improvement was greater with lurasidone (N=123) compared with placebo (N=57) on the PANSS total score (-21.3 vs. -14.9), PANSS positive subscale score (-7.0 vs. -4.1), PANSS negative subscale score (-4.9 vs. -3.7), and CGI-S score (-1.04 vs. -0.56). After 28 weeks of open-label treatment with lurasidone, additional improvement (from open-label baseline) was observed based on results of an LOCF analysis of the PANSS total score (-7.9), PANSS positive subscale score (-2.9), PANSS negative subscale score (-1.6), and CGI-S score (-0.62). Patients initially treated with double-blind placebo demonstrated greater improvement during the open-label lurasidone treatment phase, resulting in a level of improvement in PANSS total and subscale scores at week 28 that was similar to the improvement observed in the lurasidone continuation treatment group. Reasons for study discontinuation consisted of withdrawal of consent (12.8%), adverse events (11.1%), lost to follow-up (4.4%), lack of efficacy (4.4%), and other reasons (5.6%). Conclusion: Long-term treatment with lurasidone was associated with sustained improvement in psychotic symptoms as measured by the PANSS total and subscale scores this interim analysis of 28 weeks data from an open-label 24-month extension study of adolescents with a diagnosis of schizophrenia. Sponsored by Sunovion Pharmaceuticals Inc. ClinicalTrials.gov identifier: NCT01914393.

E10

CLINICAL AND ECONOMIC OUTCOMES WITH PALIPERIDONE AND ARIPIPRAZOLE LONG ACTING IN CLINICAL PRACTICE

Hodgson RE, Psychiatry, Lyme Brook Centre, Newcastle u lyme North Staffordshire, ST15 8JN rhod819147@aol.com

Introduction Paliperidone palmitate (PP) and aripiprazole long acting (AM) are depot antipsychotics that received marketing authorisation in the UK in 2011 and 2014 respectively. Medication adherence is a significant issue in people with psychosis so long acting injections (LAIs) should have theoretical advantages over oral equivalents but this is difficult to demonstrate in short randomised controlled trials. Observational studies have shown better outcomes (Tiihonen et al, 2011 AJP 168: 603-609) but generally have a primary outcome of inpatient bed use. We examined the clinical effectiveness and use of PP and AM in one mental health trust using the Health of the Nation Outcome Scale (HoNOS) as well as bed use. This tool is validated and routinely used in clinical practice in England and measures behaviours, impairments, symptoms and social functioning. Methods All patients prescribed PP/AM in North Staffordshire (population 470 000) since launch were identified and records examined for demography,

diagnosis, bed, medication use, HoNOS scores and laboratory investigations. We used a one year mirror methodology. Results 114 patients received PP (84)/AM (30) in a time frame allowing a two year follow up for PP and one for AM. 65% were male and the mean age was 40 years. Over half were detained under the 1983 Mental Health Act when the LAI was initiated. Poor adherence/effectiveness was the primary reasons for starting a LAI in 80% and mean length of diagnosis of over five years. HONOS scores reflected this with a mean total score of 15.8 (SD 7.6) before starting PP and 12.9 (SD 8.4) at two year follow up (P=0.0001). For AM the mean total score was 13.3 (SD 6.3) at initiation and 8.5 (SD 5.5) at one year follow up (P=0.0001). All subscores showed statistically significant improvement except the impairment subscale. A statistically significant reduction in bed use was seen with both LAIs which offset the drug cost threefold. All mean lipid and glucose parameters were in the normal range for both LAIs but mean prolactin for PP was raised (954 mlU/l). Conclusions Within the limitations of the methodology and sample our results show both clinical improvement and bed use. The patient population demographics were similar to that seen in clinical trials but around half were detained patients suggesting a difficult to manage population. Mean serum glucose and lipids were within the normal range which is reassuring given disquiet regarding premature mortality in this population. No sponsorship received.

E11

DIFFERENTIAL EFFECTS OF ANTIPSYCHOTIC EXPOSURE ACROSS STAGES OF REWARD PROCESSING IN A PLACEBO CONTROLLED DESIGN

Hawkins PCT, Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London De Crespigny Park London, SE5 8AF peter.hawkins@kcl.ac.uk

Vernon AC(2), Mehta MA(1)

(1) As presenting author; (2) Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King's College London, De Crespigny Park London SE5 8AF

Introduction: One putative therapeutic mechanism of antipsychotic medication is modulation of dysfunctional reward or salience processing in cortico-striatal dopaminergic pathways. Several fMRI studies have indicated antipsychotics influence regional BOLD signal during reward anticipation and outcome in people with schizophrenia (Juckel, 2016, Dialogues Clin Neurosci.; 18(1), 109–114). However, precise assessment of these effects is often complicated within patient samples due to the inherent heterogeneity of the disorder and a lack of placebo control. Furthermore, using fMRI to assess drug induced changes may be confounded by pharmacological influences on non-neuronal components of the BOLD signal, such as vascular reactivity and baseline perfusion (Bourke & Wall, 2015, Front Neurosci.; 9, 167). In this study, we attempt to account for these confounds by assessing the effect of a single dose of three commonly prescribed antipsychotics in healthy human participants during reward processing, while controlling for measures of cerebral blood flow (CBF) and vascular reactivity. Methods: Forty-two males were randomly assigned to one of two parallel groups in a double-blind, placebo-controlled, randomised, three-period cross-over study design. One group received a single oral dose of either 0.5mg, 2mg of risperidone or placebo during each visit. The other received either olanzapine (7.5mg), haloperidol (3mg) or placebo. MRI acquisition was conducted at the estimated peak plasma concentration of the drug. The Monetary Incentive Delay (MID) task was employed to assess reward processing, with contrasts of interest set to examine reward anticipation and reward/no-reward outcome. Measures of cerebral blood flow and vascular reactivity were obtained using arterial spin labelling and a breath hold task respectively, as covariates of no interest. Both whole brain permutation testing and a generalised estimating equation using a priori ROIs (striatal, amygdala, midbrain and frontal) were employed to assess drug effect. Results: Compared to placebo, risperidone and olanzapine exerted opposing effects across reward processing, with both significantly reducing activation during reward anticipation but increasing it during reward outcome ($p<0.05$). Post-hoc comparisons revealed these changes were mostly limited to the striatum during anticipation, but extended to extra-striatal areas during reward outcome. No such effect was observed for haloperidol. Conclusions: The atypical antipsychotics exerted complex divergent and region dependant effects during separate stages of reward processing, most likely due to their broad neurotransmitter profile in comparison to haloperidol, which did not alter reward related activation. By accounting for potential confounds within both the sample and the measured BOLD signal, this study has provided increased

precision of the assessment of antipsychotic effects on reward processing. This study was funded by a grant from F. Hoffmann-La Roche.

E12

PALIPERIDONE LONG-ACTING INJECTION: ONE-YEAR OUTCOMES IN CLINICAL PRACTICE

Deslandes PN, Faculty of Life Sciences, University of South Wales, Lower Glyntaff Campus, CF37 4BE paul.deslandes@southwales.ac.uk

Ward E(1), Norris K(1), Sewell RDE(1)

(1) School of Pharmacy and Pharmaceutical Sciences, Cardiff University CF10 3NB

Introduction: Paliperidone palmitate (PP) long-acting injection was recommended as a treatment option for schizophrenia in NHS Wales (UK) in 2012. The aim of this study was to assess the clinical effectiveness of PP using treatment continuation at one year as an outcome. Methods: All patients from a single health board in Wales who were initiated on PP prior to December 2014 were identified from pharmacy records. Data were collected by retrospective case-note review. Demographic factors which may have influenced outcome were analysed, and reasons for treatment discontinuation noted. For patients completing one year of treatment, inpatient stay in the 12 months prior to and following PP initiation was compared. Previous treatment with clozapine was considered an indicator of treatment refractory illness. Results: Sixty-six patients received PP, of whom two were lost to follow-up. Of the 64 patients included, 41 had a diagnosis of schizophrenia and seven had previously received clozapine. The number of continuers at six and 12 months was 44 (69%) and 40 (63%) respectively. Treatment continuation was not associated with diagnosis, age at initiation, gender, previous risperidone treatment or inpatient/outpatient status on initiation. For continuers, mean duration of inpatient stay prior to and post initiation was 83.2 ± 105.3 and 73.5 ± 103.3 days respectively (p=0.61). The most common reason for discontinuation was lack of effect (n=9). Conclusions: The proportion of patients remaining on treatment was comparable to that reported in a naturalistic study of PP (Attard et al. Acta Psychiatrica Scand 2014; 130:46-51). In contrast to the study of Attard et al (2014), inpatient status on initiation did not appear to influence treatment continuation, although patient numbers were small. Treatment continuation at six months appeared to be associated with continuation at 12 months, with only four additional patients discontinuing during the second half of the study period. Sources of funding: None.

E13

AMISULPRIDE AUGMENTATION OF CLOZAPINE FOR TREATMENT-REFRACTORY SCHIZOPHRENIA: THE AMICUS STUDY

Barnes TRE, Centre for Psychiatry, Imperial College, Du Cane Road, London, W12 0NN t.r.barnes@imperial.ac.uk

Leeson V(1), Paton C(14), Marston L(5), Osborn DP(7), Kumar R(15), Keown P(12), Zafar R(9), Iqbal K(3), Singh V(6), Fridrich P(11), Fitzgerald Z(10), Bagalkote H(13), Haddad PM(8), Husni M(4), Amos T(2)

(1) As presenting author; (2) Avon and Wiltshire Mental Health Partnership NHS Trust, Bristol; (3) Bradford District Care Trust, Bradford; (4) Central and North West London NHS Foundation Trust, London; (5) Department of Primary Care and Population Health, University College London; (6) Derbyshire Healthcare NHS Foundation Trust, Derby; (7) Division of Psychiatry, University College London; (8) Greater Manchester West Mental Health NHS Foundation Trust, Manchester; (9) Lincolnshire Partnership NHS Foundation Trust, Lincoln; (10) Manchester Mental Health and Social Care NHS Trust, Manchester; (11) North Essex Partnership University NHS Foundation Trust, Harlow; (12) Northumberland Tyne and Wear NHS Foundation Trust, Newcastle upon Tyne; (13) Nottinghamshire Healthcare NHS Foundation Trust, Nottingham; (14) Oxleas Mental Health Foundation Trust; (15) Tees, Esk and Wear Valley NHS Foundation Trust, BIllingham

In around a third of people with schizophrenia, the illness responds poorly to standard treatment with antipsychotic medication. Clozapine is the only antipsychotic medication with robust evidence for efficacy in strictly-defined treatment-resistant schizophrenia, but even then, an adequate response is seen in only

30-60% of patients. When a trial of clozapine proves to be insufficient, clinicians commonly add a second antipsychotic, although robust evidence to justify this practice, with regard to the potential benefits and risks, is lacking. The study was a multicentre, double-blind, individually randomised, placebo-controlled, 12-week trial. Eligible participants were people aged 18–65 years with treatment-resistant schizophrenia unresponsive, at a criterion level of persistent symptom severity and impaired social function, to an adequate trial of clozapine monotherapy. Interventions comprised clozapine augmentation over 12 weeks with amisulpride or placebo. Participants received 400 mg of amisulpride or one matching placebo capsule for the first 4 weeks, after which there was a clinical option to titrate the dosage of amisulpride up to 800 mg or two matching placebo capsules for the remaining 8 weeks. A total of 68 participants were randomised. There were no statistically significant differences between the amisulpride and placebo groups on mental state measures over the follow-up period. Amisulpride-treated participants were more likely to fulfil the criteria for a clinical response, OR 1.17 (95% CI 0.40, 3.42) and had a greater reduction in negative symptoms, but these non-significant, numerical differences were only evident at 12 weeks. The failure to find a significant benefit with amisulpride challenges the validity of potent dopamine D2 receptor blockade as a criterion for selecting an augmenting antipsychotic to treat clozapine-unresponsive schizophrenia. The findings support previous evidence that a clinical response to the augmentation of clozapine with a second antipsychotic may not be evident within the 4-6 weeks usually considered adequate for a trial of antipsychotic monotherapy for an acute psychotic episodes. A significantly higher proportion of participants in the amisulpride group had at least one adverse event compared with the control group (p=0.014), and these were more likely to be cardiac symptoms. Thus, comprehensive assessment of side effect burden revealed a greater side-effect burden in those participants assigned to the clozapine-amisulpride combination, which has implications for the nature and frequency of safety and tolerability monitoring of such a combination treatment in clinical practice. The limitations of the study are that it was underpowered to detect differences in the primary outcome criterion level of clinical response, so acceptance of the null hypothesis carries an increased risk of type II error. Further, the findings only apply to augmentation of clozapine with amisulpride in treatment-refractory schizophrenia and may not be generalisable to clozapine augmentation with other antipsychotic medication. This project was funded by the National Institute for Health Research (Health Technology Assessment programme: project number 08/116/12).

E14

AUDIT ON BASELINE MONITORING SERUM PROLACTIN

Jayakumar A, (Acute Adult) General Psychiatry; inpatient unit, George Bryan Centre, Plantation Lane Tamworth, B78 3NG m1000202aj@gmail.com

Krishnan V(1)

(1) Consultant Psychiatrist, George Bryan Centre, Tamworth, B78 3NG

Introduction: National Institute of Health and Care Excellence guidelines for Psychosis and Schizophrenia recommend that all patients initiated on an antipsychotic should have baseline Prolactin levels measured in addition to other investigations, NICE 2014. This is due to established knowledge that antipsychotic medication can have adverse metabolic effects such as hyperprolactinaemia. In addition to this, the Maudsley prescribing guidelines provide safe advice on investigating and managing hyperprolactinaemia, Taylor D et al, 2015. Aim: To identify the proportion of patients, who have had baseline serum prolactin levels measured (as recommended by NICE guidelines) and physical health examined, prior to starting treatment. Methodology: This was a retrospective study where data was collected from the hospital's electronic notes system (RiO) The RiO administrative team generated a list of 138 patients who were patients admitted to an inpatient unit for the first time between 1st December 2015 to 30th November 2016. An audit tool was created which was a combination of standards from the NICE guidelines and Maudsley Guidelines. A pilot was carried out and modifications were made to the audit tool. Results: 44 out of the 138 newly admitted patients had a diagnosis of psychosis and were started on an antipsychotic medication. 25 patients from the cohort of 44 had their baseline serum prolactin measured; therefore there was a 57% level of compliance based on clinical guidelines. 12 out of the 25 patients had their baseline serum prolactin raised above the stated reference range, and merely 5 of those patients had follow-up

actions as recommended by the Maudsley Prescribing Guidelines. Finally, 39 out of the 44 patients had their physical health examinations prior to starting treatment. Conclusions: The sample size was a good representation of general adult inpatient unit. The overall outcome shows that there was relatively poor compliance in measuring baseline prolactin, and poor compliance in fulfilling recommended actions for patients with raised serum prolactin levels. In order to achieve 100% compliance against the standard, there must be an increase in awareness to junior doctors during their induction period and during daily ward rounds. This audit should be re-audited in December 2017, to ensure that the inpatient unit achieves 100% compliance. This audit was carried by George Bryan Centre, Tamworth, and there was no funding involved.

E15

TREATMENT OF DEPRESSION IN SCHIZOPHRENIA: IMPORTANCE AND THERAPEUTIC CHALLENGES

Gregory A, Psychiatry, University of Birmingham, The Barberry, University of Birmingham, 25 Vincent Drive Edgbaston Birmingham, B152FG r.upthegrove@bham.ac.uk

Mallikarjun P(1), Upthegrove R(1)

(1) As presenting author

Introduction: Depression in schizophrenia predicts poor outcomes, including suicide, yet the effectiveness of antidepressants for its treatment remains uncertain. The aim of this study was to synthesise the evidence of the effectiveness of antidepressants for the treatment of depression in schizophrenia. Methods: Following Prisma guidelines, multiple databases were searched for trials investigating the effectiveness of antidepressant treatment for people with schizophrenia and depression. Inclusion criteria included participants aged over 18 years with schizophrenia or related psychosis with a depressive episode. Papers were quality assessed used the Cochrane risk bias tool. Data was extracted with meta-analyses performed for risk difference and standardised mean difference of all antidepressants, antidepressant class and individual antidepressant where sufficient studies allowed. Results: 26 moderate to low quality trials met inclusion criteria. In meta-analysis a significant risk difference was found in favour of antidepressant treatment, with a number needed to treat of 5 (95% CI 4-9). Studies using tools specifically designed to assess depression in schizophrenia showed a larger effect size. However, after sensitivity analysis standardised mean difference of all antidepressants did not suggest a significant improvement in depression score at end-point, neither did any individual antidepressant class. Conclusion: Antidepressants may be effective for the treatment of depression in schizophrenia, however the evidence is mixed and conclusions must be qualified by the small number of low or moderate quality studies. Further sufficiently powered, high quality studies are needed. no sponsorship was received for this study.

E16

INCREASED DNA METHYLATION AT A TRANSCRIPTION FACTOR BINDING SITE IN THE GENE FOR THE 5-HT1A RECEPTOR CORRELATES WITH NEGATIVE SYMPTOMS IN FIRST EPISODE PATIENTS.

Reynolds GP, BMRC, Sheffield Hallam University, Sheffield UK, S1 1WB gavin.reynolds@hotmail.com

Fachim HA(1), Tang H(1), Zeng L(2), Yang JZ(2)

(1) BMRC, Sheffield Hallam University, Sheffield S11WB; (2) Second Affiliated Hospital, Kunming Medical University, Kunming, China

Poor negative symptom response is a major limitation of antipsychotic treatment in schizophrenia. There is substantial individual variability in negative symptoms and their treatment response; a functional polymorphism, rs6295, in the 5-HT1A receptor gene (HTR1A) contributes to this variability (Reynolds et al, 2006, Am J Psychiat 163, 1826-1829). The DNA sequence containing rs6295 is rich in methylation (CpG) sites; CpG methylation is an epigenetic factor that, like the rs6295 polymorphism, can modify transcriptional control. We previously found that DNA methylation at a specific CpG site (CpG13) in a recognition sequence for HES transcriptional repressors close to the rs6295 polymorphism correlates with baseline PANSS negative symptom sub-score and change in this score following antipsychotic treatment (Tang et al, 2014, Pharmacogenomics 15, 1599-1609). The current study aimed at replicating this finding

in a further sample of people with schizophrenia. DNA methylation in the sequence around the rs6295 polymorphism was determined in blood-derived DNA from a series of subjects with schizophrenia assessed for PANSS before and after 12 weeks risperidone treatment. After extraction, genomic DNA from blood collected at treatment initiation was bisulfite-modified and the percentage methylation at each of four sites plus the polymorphism site was determined by pyrosequencing. Symptoms and their changes with time were determined by PANSS items divided into five symptom factors; these scores were correlated with CpG methylation at each site. CpG methylation was successfully determined in 45 subjects, of whom 18 were drug-naïve, first episode patients. No significant correlations between symptoms scores and methylation were found in the full series. However, in the drug-naïve subgroup, strong and highly significant correlations were identified between methylation at CpG13 and both baseline negative factor subscore (p=0.001) and its change (p=0.008) following initial antipsychotic treatment. The effect on symptom change did not remain after correction for the association with baseline score. These results confirm, in a small independent sample, how the extent of methylation at a specific site in the promoter sequence of HTR1A is related to negative symptom severity in a first-episode Chinese sample, although we failed to replicate in this sample the specific effect of methylation on treatment response in both total PANSS and negative symptoms previously observed. These findings suggest HTR1A promoter methylation, and hence perhaps gene expression, may be related to negative symptom severity in first episode patients, and further indicate the role of the 5-HT1A receptor in negative symptoms. No financial sponsorship was received for this study.

E17

INFLAMMATORY MARKERS' ROLE IN SCREENING FOR PHYSICAL COMORBIDITIES IN PATIENTS AT FIRST EPISODE OF PSYCHOSIS

Nettis MA, Psychological Medicine, King's College London, G.33.75 Wohl Maurice Institute Cutcombe road London, SE5 9RT maria.nettis@kcl.ac.uk

Kolliakou A(3), O'Connor J(3), Bonaccorso S(3), Gardner-Sood P(3), David A(3), Gaughran F(3), Pariante CM(1), Murray R(2), Dazzan P(3), Mondelli V(1)

(1) As presenting author; (2) Department of Psychosis Studies, IoPPN, King's College London, SE58AF, London; (3) Dept of Psychosis Studies, IoPPN, King's College London, SE5 8AF, London

Introduction High levels of inflammation have been recently found in patients at their First Episode of Psychosis (FEP). These individuals commonly develop later metabolic abnormalities and cardio-vascular diseases (Russel et al., 2015, Brain, Behavior and Immunity, Vol 49, 25-29). This longitudinal study investigated how baseline C-reactive protein (CRP), categorized accordingly with guidelines for cardiovascular risk screening (Cozlea et al., 2013, Current Health Sciences Journal, Vol4, 226-231), can influence the metabolic outcome, at 3 and 12 months of follow-up in FEP. Methods Sixty patients at their onset of psychosis were assessed at the time they were accessing clinical care for the first time (T1), and again after 3 (T2) and 12 (T3) months. At each time, we collected anthropometric measures as well as fasting blood samples to investigate lipid profile and gluco-metabolic parameters (glycated hemoglobin (HbA1c), fasting glucose). CRP levels were categorized as follows: CRP <1 mg/L=low cardiovascular risk; 1mg/L > CRP>3 mg/L = medium cardiovascular risk; CRP ≥3mg/L = high cardiovascular risk. A one-way ANOVA, followed by Bonferroni post-hocs, was performed using baseline CRP levels as independent variable and metabolic parameters at T2 and T3 as dependent variables. Results Results showed that patients with higher cardiovascular risk at T1 (CRP ≥3 mg/L), had significantly higher fasting glucose values (mean ±SD, 6.5 ± 3.1 mmol/L) at T2, compared with patients with medium (4.7 ± 0.4 mmol/L, p= 0.007) and low cardiovascular risk (4.7 ± 0.5 mmol/L, p= 0.002). A similar pattern was found for fasting glucose values at T3, with participants with high baseline cardiovascular risk having higher fasting glucose levels (mean ±SD, 6.6 ± 3.03 mmol/L, p=) than both the other two categories (medium risk: 4.6 ± 0.4 mmol/L, p=0.035; low risk: 4.7 ± 0.7 mmol/L, p=0.033). Conclusion These findings highlight the importance of inflammation markers to early identify psychiatric patients at risk of physical health comorbidities. This research has been 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.

E18

THE EFFECTS OF Δ9-TETRAHYDROCANNABINOL (THC) ON EMOTIONAL PROCESSING: A SYSTEMATIC REVIEW

Lees RH, Institute of Cognitive Neuroscience, UCL, Alexandra House, 17-19 Queen Square, Bloomsbury, London, WC1N 3AR rachel.lees.16@ucl.ac.uk

Petrilli K(1), Hindocha C(4), Howes O(6), Curran V(5), Freeman T(3), Bloomfield M(2)

(1) As presenting author; (2) Division of Psychiatry, Maple House, London, UCL W1T 7BN; (3) National Addiction Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, SE5 8BB; (4) Research Department of Clinical, Educational and Health Psychology, University College London, WC1E 7HB; (5) Research Dept of Clinical, Educational and Health Psychology, Faculty of Brain sciences, UCL, WC1E 7HB; (6) Robert Steiner MRI Unit, Hammersmith Hospital, Imperial College London, W12 0HS

Heavy cannabis use is associated with a range of negative mental health outcomes including increased risk of depression and psychosis. The neurobiological mechanisms underlying this vulnerability remain unknown. Δ9-tetrahydrocannabinol (THC), the main psychoactive ingredient of cannabis, can induce both psychotic symptoms and negative emotions. We therefore sought to review the literature on THC and emotional processing. We used PRISMA guidelines to systematically review the literature. We searched the Web of Science and PubMed for terms related to THC and emotional processing, including human and animal studies. We excluded studies that did not measure outcomes of emotional processing. The studies in animals consisted of acute challenge and repeated THC administration, and measured emotional processing used in animal models of anxiety and depression. The studies in humans also included acute THC challenge studies, as well as studies that looked at emotional processing in chronic cannabis users. Nine rat studies and 18 human studies are included in this review. Common tasks in animals included the elevated plus maze to measure anxiety, and the forced swim test to measure depressive behaviour. Measures of emotional processing in humans were focused around human facial affect stimuli, including tasks of recognition of emotion and implicit decision making. Human acute THC studies suggest that THC impairs recognition of emotion, with a specific deficit for threat-related emotion. Human studies of chronic users suggest that these deficits in emotion recognition are not a transient effect of THC, as users consistently showed impaired performance across a range of tasks. Neurally, THC appears to affect amygdala reactivity to emotional stimuli in humans, including its functional connectivity with other regions such as the prefrontal cortex, though the direction of effect is unclear. Rat studies suggest a detrimental effect on measures of both anxiety and depression, with a gender effect as these deficits appear to affect female more than male rats. Overall, we found that emotional processing is negatively affected by an acute THC challenge as well as by chronic cannabis use. These findings may explain how THC increases the risk of mental illness, via mediating the response to emotional stimuli in the environment. More research is needed in this area of research to further assess this relationship. In particular, task differences between animal and human research make it difficult to translate the findings, therefore translational experiments are required in order to bridge this gap. No sponsorship received for the study.

E19

IMMUNE DYSFUNCTION, DEPRESSIVE AND NEGATIVE SYMPTOMS IN SCHIZOPHRENIA

Krynicki CR, Dept of Psychiatry, Institute of Clinical Sciences, Univ of Birmingham, National Centre for Mental Health, The Barberry, 25 Vincent Drive, Birmingham., B15 2FG c.krynicki@bham.ac.uk

Upthegrove R(1), Nikkheslat N(2), Giordano A(2), Pariante CM (2), Deakin JFW(3), Dazzan P(2)

(1) Department of Psychiatry, Institute of Clinical Sciences, College of Medical and Dental Sciences, University of Birmingham, National Centre for Mental Health, The Barberry, 25 Vincent Drive, Birmingham, B15 2FG; (2) Department of Psychosis Studies, PO 40, Institute of Psychiatry, De Crespigny Park, London, SE5 8AF; (3) Neuroscience & Psychiatry Unit, Faculty of Biology, Medicine and Health, G.907 Stopford Building

Introduction: The biological distinction between positive and negative symptoms of schizophrenia is chiefly validated by the lack of response of negative symptoms to antipsychotic treatments. The nature of

negative symptoms remains uncertain. One suggestion is that avolition-apathy and diminished-expression underpin negative symptoms but both can be a feature of depressive illness. However, factor analytic studies suggest that depression is dissociable from negative symptoms. Chronic immune dysfunction has been implicated in both psychotic and depressive illnesses mainly on the basis of increased circulating pro-inflammatory cytokines (such as IL-6, TNF- α) and acute phase proteins (such as CRP). Our aim was to investigate whether longitudinal changes in pro-inflammatory cytokines differentially relate to depressive or to negative symptoms (avolition-apathy or diminished-expression), in those within three years of symptom onset. Method: 207 participants with psychosis were recruited across the UK as part of a clinical trial of the anti-inflammatory antibiotic minocycline, Benefits of Minocycline on Negative Symptoms (BeneMin) study. Negative symptoms (separated into sub-domains) were assessed using PANSS interview ratings and depression using Calgary Depression for Schizophrenia Scale. Participants were followed up over 12 months, with blood samples being taken for cytokine assays: IL-6, CRP and TNF-α at baseline, 6 and 12 months, and repeated clinical measures at 2, 6, 9 and 12 months. Five linear mixed effect models were constructed; two to assess the association between depression and avolition apathy, and diminished expression, and three to assess the association between markers of inflammation and each clinical variable. Results: Longitudinal depression scores were associated with avolition-apathy at 12 months (B = .06, p < .01) but not with expressive-deficits at 12 months (B = .04, p = .07). Depression was associated with greater CRP (B = .34, p < .01) and TNF-α (B = -1.23, p < .01) concentrations at 12 months. However, avolition-apathy although associated with depression, was not associated with any marker of inflammation. Conversely, diminished expression was not predictive of depression but both depression (B = -1.23, p < .01) and diminished expression (B = .82, p < .01) were associated with increased TNF-α concentrations over 1 year. Discussion: Depression in schizophrenia may be related to negative symptoms via the avolition-apathy sub-domain. However, this association is small and depression in schizophrenia may be largely independent of negative symptoms. These findings suggest that there are separate biological drivers underlying the sub-domains of negative symptoms, with pro-inflammatory markers being associated with diminished-expression and depression, but not avolition-apathy. Data used in this study was obtained from the BeneMin trial. The BeneMin trial was an NIHR-EME funded study.

E20

INTERACTIVE EFFECTS OF EARLY LIFE STRESS AND CACNA1C GENOTYPE ON CORTISOL AWAKENING RESPONSE

Klaus K, School of Psychology, Univ of Lincoln, Brayford Pool, Lincoln, UK, LN7 6TS kklaus@lincoln.ac.uk

Butler K(1), Gutierrez H(2), Durrant SJ(1), Pennington K(1)

(1) As presenting author; (2) School of Life Sciences, Univ of Lincoln, Brayford Pool, Lincoln, UK, LN7 6TS

Recent research shows that genetic vulnerability, in interaction with environmental factors such as early life stress (ELS), could lead to hypothalamic-pituitary-adrenal (HPA) axis dysfunction and consequently contribute to the development of mental health disorders (Holtzman et al., 2013, Neuroscience, 249, 172-191). The CACNA1C gene encoding the α1C subunit of the L-type voltage-dependent calcium channel $Ca_V1.2$ has been implicated in mental health disorders such as schizophrenia (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013, Lancet, 381, 1371-1379). L-type voltage gated calcium channels are also sensitive to the effects of glucocorticoids (Joëls & Karst, 2012, Cell Calcium, 51, 277-283), therefore potentially contributing to dysfunctional stress response system. This study aimed to investigate the role of ELS and its interaction with CACNA1C rs1006737 in affecting cortisol awakening response (CAR), an indicator of HPA axis function. Salivary cortisol measures were taken from 109 healthy adult males (aged 21-63) on two consecutive days at awakening and 30 minutes later. ELS was assessed using the Childhood Traumatic Events Scale (Pennebaker & Susman, 1988, Social Science and Medicine, 26, 327-332). The data were analysed using two-way analysis of covariance, with CACNA1C rs1006737 genotype (risk allele A carriers vs GG) and childhood trauma category (trauma/no trauma) as fixed factors and baseline cortisol levels, sleep duration, waking time and age as covariates of non-interest. The results revealed significant main effects of CACNA1C genotype ($F_{1,101}=4.246$, p=.042), childhood trauma before the age of 17 ($F_{1, 101}=10.116$, p=.002), and a genotype by trauma group interaction ($F_{1, 101}=5.141$, p=.025) on CAR, whereby

non-risk allele carriers (GG) who had experienced ELS showed higher CAR compared to the other groups. The main effects of genotype, childhood trauma, and their interaction was even more pronounced if the stress was experienced before adolescence, i.e. before the age of 13 (F1, 100=7.311, p=.008; F1,100=11.138, p=.001; F1, 100=6.877, p=.010 respectively). Current perceived stress, anxiety and depression levels were not associated with CAR, p>.05 in all cases. This study is the first to provide evidence that the effect of ELS on CAR may be mediated via CACNA1C rs1006737 genotype, whereby risk allele carriers who have experienced trauma may have a blunted CAR previously associated with the risk for developing psychosis (Day et al., 2014, Schizophrenia Research, 158, 25-31). Future work should further clarify the role of calcium channels and their interaction with stress in HPA axis function and how this might contribute towards psychopathology in mental health disorders. This work was supported by the University of Lincoln's College of Social Science Research Fund, the School of Psychology at the University of Lincoln and WiSE Academic Returners' Research Fund (R2F) awarded to KP and a University of Lincoln College of Social Science PhD studentship to KK.

E21

(POMH-UK) TOPIC ON PRESCRIBING ANTIPSYCHOTICS FOR CHILDREN AND ADOLESCENTS

Gupta V, CAMHS, TEWV, Stockton CAMHS Viscount House Falcon Court Westland Way Preston Farm Industrial Estate Stockton on Tees, TS18 3TS veenugupta@nhs.net

Hegarty A(1)

(1) TEWV

Background POMH-UK runs national audit-based quality improvement programmes (QIPs). In 2014, TEWV participated in POMH-UK Quality Improvement Programme Topic 10c on prescribing antipsychotics for children and adolescents. The response rate for the National audit was low and the results indicated limited monitoring of physical health parameters and extrapyramidal side effects. As part of the action plan arising from that audit, it was agreed that the Children and Young People's Service would complete the audit cycle. The criteria and standards were based on NICE Clinical Guideline 155 Psychosis and Schizophrenia in Children and Young People. Aims & Hypothesis Evaluating the outcomes after introduction of a new monitoring tool for Prescribing Observatory for Mental Health (POMH-UK) on prescribing antipsychotics for children and adolescents. Methods A new proforma was introduced and the audit tool sent to all CAMHS prescribers (medical, non-medical, inpatient and community) for patients under the age of 21 years who were prescribed antipsychotic medication. Data was collected between 17th February 2015 and 1st April 2015 and was analysed by the Clinical Audit and Effectiveness Team. Results A total of 62 patient records were assessed. At Trust level there was evidence of good practice in documenting an explicit rationale for prescribing antipsychotic medication. 100% of patients prescribed antipsychotics for fewer than 3 months had baseline weight/BMI, blood pressure and pulse recorded. This was an improvement from 67% in the 2014 audit. The results show a mixed picture when looking at individual teams. 5 teams achieved a total of more than 80% compliance across all standards, 7 teams achieved 50-79% and 3 teams achieved fewer than 49%. In general the monitoring of blood glucose and lipids remains poor both at baseline in those prescribed antipsychotics for fewer than 3 months (57% and 43% respectively), and as part of ongoing monitoring for those prescribed antipsychotics for more than 3 months (52% and 48% respectively). Conclusions CAMHS teams should design and implement a physical health monitoring tool to improve monitoring of physical health parameters and extrapyramidal side effects. These audit findings should be disseminated to the CAMHS teams. Funding: There was no financial sponsorship for this study.

E22

WHAT DOES AUGMENT THE RISK TO USE CANNABIS ON AN EVERYDAY-BASIS IN PSYCHOTIC PATIENTS?

Ferraro L, Biomedicina Sperimentale e Neuroscienze Cliniche (BioNeC), University of Palermo, via gaetano la loggia, 1, 90124 laura_ferraro@hotmail.it

DiForti M(3), Capuccio V(4), Quattrone D(3), Tripoli G(3), Seminerio F(1), Sartorio C(1), Sideli L(1), La Cascia C(1), La Barbera D(1), Murray RM(2)

(1) As presenting author; (2) Psychosis Studies, Institute of Psychiatry, Kings College London, De Crespigny Park London SE5 8AF; (3) Psychosis Studies, Institute of Psychiatry, Kings College London, De Crespigny Park London SE5 8AF; (4) Scienze Economiche, Aziendali e Statistiche (DSEAS), Università degli Studi di Palermo, Viale delle Scienze, Palermo

Introduction There is strong evidence that risk of psychosis is augmented by cannabis use. In a recent analysis, the strongest predictor of case-control status was daily use of high-potency cannabis, i.e. the ORs of psychosis for skunk-users increased with the frequency of use (Di Forti et al., 2015, Lancet Psychiatry 2, 233–238). We know also that people with first episode psychosis (FEP) who smoked cannabis in their lifetime are less neuropsychologically impaired than non-users i.e. they have better premorbid-IQ (Ferraro et al., 2013 Schizophr. Res. 150, 129–135). In this study we tested if premorbid adjustment and cognition modulate the risk to be an everyday-user along with age at first cannabis-use and % of THC in cannabis used. Methods The sample comprised 834 FEP cannabis-using and non-using patients from different European countries and 1.061 healthy controls, as part of the EUGEI-STUDY. A logistic regression was computed, using frequency of cannabis use among those who reported to have used cannabis in their lifetime, as an outcome variable in order to estimate the risk of being an everyday-user or a less-than-everyday user, taking into account a list of predictors: socio-demographics, age at first cannabis-use, absolute % of THC, premorbid social factor (PSF), premorbid academic factor (PAF), from the Premorbid Adjustment Scale (PAS) and the four scales of WAIS-brief. Results The risk to be an everyday-smoker was higher for cases, in interaction with age at first use, i.e. while controls' risk of everyday use diminished when age at first use increases, this is not true for cases, whose risk remained high even at increased age at first use (OR=1.2, p=0.001, CI 95% 1.09, 1.45). A lower premorbid academic adjustment (OR=0.8, p=0.040, CI 95% 0.68, 0.99) and higher premorbid social adjustment before 16 years (OR=1.6, p=0.019, CI 95% 1.08, 2.60) increased the risk to be an everyday cannabis-user. However, higher working memory scores reduced the risk related to higher premorbid sociability (OR=0.9, p=0.021, CI 95% 0.90, 0.99). As expected, THC concentration >10% was associated with a 2 fold increased risk to be an everyday-smoker (OR=1.8, p=0.001, CI 95% 1.29, 2.60). Conclusions The predictors of everyday cannabis-use were lower premorbid academic adjustment but higher sociability before 16 years, the latter moderated by a higher working memory. An earlier age at first use was the most relevant risk factor for being cannabis everyday-users in psychotic subjects. No sponsorship for this study was received.

E23

HPA-AXIS FUNCTION DIFFERS IN CLINICAL AND NON-HELP-SEEKING POPULATIONS WITH AUDITORY VERBAL HALLUCINATIONS

Baumeister D, Department of Psychology, Institute of Psychiatry, Psychology & Neuroscience, King's College London, 4.04 Addiction Sciences Building 4 Windsor Walk, SE5 8BB david.baumeister@kcl.ac.uk

Chadwick P(1), Howes O(2), Peters E(1)

(1) Henry Wellcome Building, Department of Pychology, IoPPN, KCL, SE5 8AF; (2) Main Building, Department of Psychosis Studies, IoPPN, KCL, SE5 8AF

Introduction Psychosis is associated with several alterations of neuroendocrinological stress function, including blunted stress-reactivity and diminished negative feedback capacity of the hypothalamic-pituitary-adrenal axis. The present study is, to our knowledge, the first to examine how altered stress-physiology specifically relates to auditory verbal hallucinations (AVHs), one of the most frequent and distressing symptoms of psychosis, and how such alterations relate to need for care. Methods Twenty

psychosis patients with AVHs (C-AVHs), 25 members of the general populations with AVHs yet no need for care (N-AVHs), as well as 23 healthy controls (HCs) were recruited for the present study. Salivary cortisol was measured to assess the acute reaction to a psychophysiological stress paradigm, as well as to the dexamethasone suppression test, a measure of negative feedback capacity. Results C-AVHs were indistinguishable from HCs in their overall cortisol release during the stress paradigm, whilst N-AVHs showed significantly lower release than both C-AVHs and HCs. However, C-AVHs showed no increase in cortisol in response to the stressor, in contrast to N-AVHs and HCs. Negative feedback capacity significantly differed across groups, with C-AVHs showing the highest rate of non-suppression in response to dexamethasone. Conclusions Our results demonstrate that alterations of the hypothalamic-pituitary-adrenal axis are present in psychosis patients with AVHs, in a manner consistent with that of psychosis patients in general. Whilst alterations in stress-function are present in individuals with AVHs yet no need for care as well, the patterns appear different between the two groups, potentially alluding to protective differences in HPA-function in this group. These findings add to the growing literature highlighting the complexity of neuroendocrine alterations of psychosis, and underline the need to further detail the functional implications of neuroendocrine stress function in psychosis. Sponsorship D.B. receives funding support from a Medical Research Council and King's College London (KCL) PhD studentship. O.H. has received funding by the Medical Research Council-UK (no. MC-A656-5QD30), Maudsley Charity (no. 666), Brain and Behavior Research Foundation, Wellcome Trust (no. 094849/Z/10/Z) and the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. E.P. has received funding from the NIHR Biomedical Research Centre at South London.

E24

DIFFERENTIAL INVOLVEMENT OF OXYTOCIN AND V1A RECEPTORS IN THE THERMOREGULATORY, SEDATIVE AND PROSOCIAL EFFECTS OF OXYTOCIN IN THE RAT

Fone KCF, School of Life Sciences, The University of Nottingham, Queen's Medical Centre Nottingham, NG7 2UH kevin.fone@nottingham.ac.uk

Williams S(1), Edwards A(1), King MV(1)

(1) School of Life Sciences University of Nottingham

The neuropeptide oxytocin enhances prosocial behaviour and social cognition and has been proposed as a potential therapy for autism and schizophrenia. In rats, systemic injection of high doses of oxytocin produce hypothermia and hypoactivity (Hicks et al, 2014 Br J Pharmacol 171:2868–2887; Klenerova et al, 2009 J Physiol Pharmacol 60:57-62) but the mechanism mediating these effects is uncertain. Oxytocin has high affinity for both the oxytocin and V1A receptor. While the V1A receptor mediates cardiovascular changes, it is unclear which receptor mediates hypothermia and hypoactivity. This study characterises the pharmacology of oxytocin-induced hypothermia and hypolocomotion using selective oxytocin (L368,899) and V1A (SR49059) receptor antagonists. Two groups of adult male Lister hooded rats (175-200g Charles river UK, n=12 each) were implanted with subcutaneous temperature microchips (Bio-Thermo idENICHIP; AnimalCare Ltd) 48h before behavioural measurement in infra-red activity boxes. To identify an oxytocin dose which elicits hypothermia, rats received oxytocin (0.03, 0.1 or 0.3mg/kg) or saline (1ml/kg s.c.) after 30min habituation. For the antagonist study, rats were habituated for 15min before administering L-368,899 (2mg/kg i.p.), SR49059 (1mg/kg i.p.) or vehicle (Saline+5%DMSO 2ml/kg i.p.) and 15mins later received oxytocin (0.3mg/kg s.c) or saline (1ml/kg s.c.). In both groups activity was recorded in 5min epochs and body temperature every 15min for 2h (every rat receiving every drug combination at 7d intervals) and data analysed by repeated measures AVOVA with Bonferroni post-hoc. Only the highest dose of oxytocin (0.3mg/kg) caused hypothermia 30-60min post-injection (ANOVA drug x time interaction $F(21,308)=14.29$, $p<0.0001$; $p<0.001$ approximately 2oC lower than all other groups) and tended to reduced cumulative ambulation from vehicle during 30min post-injection (not significant). SR49059 significantly attenuated oxytocin-induced hypothermia ($p<0.01$-$p<0.001$ 30-60min post injection, versus Veh-Oxy) while L-368,899 had no significant effect: ANOVA oxytocin x antagonist x time interaction $F(14,462)=3.035$ $p<0.0001$. Neither antagonist, oxytocin or V1A, attenuated oxytocin-induced hypolocomotion (post-injection

mean+sem counts being; Veh-Veh (930+63), Veh-Oxy (634+64), SR49059-Veh (1038+87), L368,899-Veh (949+77), SR49059+Oxy (608+46), L368,899+Oxy (638+45); all three oxytocin groups being significantly less than Veh-Veh. High doses of oxytocin produce hypothermia in rats by activating vasopressin V1A receptors but these are not involved in producing hypoactivity, suggesting thermoregulatory and sedative effects are mediated by distinct neural pathways and/or receptor mechanisms. Only higher doses of oxytocin than mediated prosocial effects (Kohli et al. this meeting) caused hypothermia and hypoactivity, so it may be possible to dissociate these side-effects from beneficial prosocial effects in any treatment of CNS disorders. BBSRC funded.

E25

THE GLP1-R AGONIST LIRAGLUTIDE IMPROVES COGNITION AND RESTORES BRAIN METABOLISM IN NEUREXIN-1 A HETEROZYGOUS MICE.

Whittingham-Dowd JK, Division of Biomedical and Life Sciences, Lancaster University, Division of Biomedical and Life Sciences, Faculty of Health and Medicine, Lancaster University, Lancaster, LA1 4YQ j.whittingham-dowd@lancaster.ac.uk

Hughes R(2), Bristow G(2), Clapcote SJ(1), Dawson N(2)

(1) 2.Institute of Membrane and Systems Biology, University of Leeds, Leeds LS2 9JT.; (2) As presenting author

Introduction: Schizophrenia (SZ) and Type 2 Diabetes mellitus (T2DM), characterised by insulin resistance, have a shared genetic basis (Lin & Shuldiner. 2010. Schizophr Res. 123:234). Deficient insulin signalling may contribute to cognitive deficits seen in SZ (Cohn et al. 2006. Can J Psychiatry. 51:382). Glucagon-like peptide-1 receptor (GLP-1R) agonists, such as Liraglutide, are used to improve insulin signalling in T2DM patients and may be effective for the treatment of the cognitive deficits seen in SZ. Here we test the ability of Liraglutide to improve cognition and brain metabolism in mice heterozygous (Hz) for the SZ risk gene Neurexin-1α (Nrxn1α) (Rujescu et al. 2009. Hum Mol Genet. 5: 988). Methods: Nrxn1α Hz mice were treated with either Liraglutide (Lg, n=14, 25 nmol/kg/day intraperitoneally for 21 days) or vehicle (V, n=13, saline, 2ml/kg) with wild-type (WT) littermates used as controls (V, n=14, Lg, n=19). Locomotor activity was analysed in the open field for 15 minutes and mice were tested in the novel object recognition test (NORT) with a 1 hour delay. Cerebral metabolism was assessed using 14C-2-deoxyglucose functional brain imaging (WT; V, n=10, Lg, n=10, Nrxn1α Hz; V, n=10, Lg, n=9). Data were analysed using ANOVA with post-hoc Tukey's HSD. Results: Nrxn1α Hz mice showed hyperlocomotor activity, evidenced by an increase in distance moved ($p<0.01$), movement duration ($p<0.01$) and velocity ($p<0.01$), in the open field. This hyperactivity was not significantly modified by Liraglutide treatment. We found no evidence for altered anxiety-like behaviour in Nrxn1α Hz mice, with the animals spending a similar amount of time in the central zone of the open field. In the NORT vehicle-treated Nrxn1α Hz mice were not able to significantly differentiate between the novel and familiar object while WT controls spent significantly more time investigating the novel object ($p<0.01$). By contrast, Nrxn1α Hz mice treated with Liraglutide spent significantly more time exploring the novel object ($p<0.01$) showing that the deficit was reversed by Liraglutide treatment. In terms of brain metabolism, we found that Nrxn1α Hz mice treated with vehicle showed significant hypometabolism in the prelimbic ($p<0.05$) and entorhinal cortex ($p<0.05$) that was not seen in Nrxn1α Hz receiving Liraglutide treatment ($p<0.05$ genotype x treatment interaction). Conclusions: These data show that Nrxn1α Hz mice have a deficit in learning and memory and alterations in cerebral metabolism relevant to SZ. These deficits are effectively rescued by Liraglutide treatment. Thus these data support the therapeutic potential of GLP-1R agonist for the treatment of the cognitive deficits seen SZ. Financial Support: These studies were supported by The Royal Society.

E26

EFFECT OF NICOTINIC ALPHA 7 RECEPTOR AGONIST AND POSSITIVE ALLOSTERIC MODULATORS ON COGNITIVE SYMPTOMS IN SUBCHRONIC MK-801 MODEL OF SCHIZOPHRENIA IN RATS

Unal G, Department of Pharmacology and Psychopharmacology Research Unit, Marmara University, Faculty of Pharmacy, T?bbiye cad. No:49 Haydarpa?a, ?stanbul, Turkey, 34668 gokhan.unal@marmara.edu.tr

Aricioglu F(1), Hazar-Yavuz AN(1), Zortul H(1)

(1) Marmara University, Faculty of Pharmacy, Department of Pharmacology and Psychopharmacology Research Unit, Istanbul – Turkey

Introduction: Colinergic nicotinic alpha-7 receptors (alpha-7 NAChR) has became an important target for schizophrenia after demontrating deficits of alpha-7 NAChR in cognition related regions in postmortem brains. Alpha-7 NAChR full/partial agonists directly stimulates this receptors while possitive allosteric modulators (PAMs) indirectly facilitates neurotransmission. Electrophysiological studies showed that Type I PAMs increased agonist-evoked peak amplitude while Type II PAMs increased either peak amplitude or duration. (A.V. Terry Jr. et al, 2015, Biochemical Pharmacology, 97, 388–98). We aimed to investigate effects of partial agonist (A-582941), Type I PAM (CCMI) and Type II PAM (PNU-120596) in subchronic MK-801 models of schizophrenia in rats. Methods: Male Wistar Hannover rats were grouped as Control, MK-801 (0,2mg/kg), MK-801+A-582941 (1mg/kg), MK-801+CCMI (1mg/kg), MK-801+PNU-120596 (3mg/kg) and MK-801+Clozapine (5mg/kg) (n=8-10). MK-801 was injected (i.p.) twice a day for 7 days. After a week washout period, treatment groups received (i.p.) A-582941, CCMI, PNU-120596 or Clozapine for 10 days. Novel object recognition test (NORT) and Morris's water maze (MWM) test were conducted at 6th and 6-10th days, respectively. Results: In NORT, MK-801 decreased discrimination index (DI) compared to control group ($p<0.01$). Clozapine, A-582941 and PNU-120596 treatments increased DI while CCMI had no effect ($p<0.01$, $p<0.01$ and $p<0.001$ respectively). In MWM learning period, latency to finding platform in MK-801 group was longer than control group at first, second and fourth days ($p<0.05$, $p<0.001$, $p<0.05$, respectively). Clozapine (on 3th and 4th day), A-582941 (on 2nd day), CCMI (on 1st, 2nd and 3th day), PNU-120596 (on 2nd, 3th and 4th day) treatment significantly decreased platform finding latency compared to MK-801 group ($p<0.05$). In MWM probe test, MK-801 decreased the time in platform arena ($p<0.01$) whereas Clozapine and CCMI groups spent longer time compared to MK-801 group ($p<0.01$). Conclusion: Although main target of alpha-7 NAChR partial agonist, Type I and II PAMs is enhancing cholinergic transmission, our results clearly showed an improvement in MK-801-induced cognitive deficits of schizophrenia in a different manner. These differences might be either due to their pharmacological profile or receptor densities in the regions which are responsible for the control of visual and spatial memory. There was no financial sponsorship in this study.

E27

DYSREGULATED GABAERGIC EXPRESSION IN RODENT CYFIP1+/- KO MODELS, BUT NOT IN OTHER GENETIC OR NEURODEVELOPMENTAL MODELS OF RISK FOR PSYCHIATRIC ILLNESS

Trent S, Neuroscience & Mental Health Research Institute, Cardiff University, Neuroscience & Mental Health Research Institute 3.40 (Fellows Office) Hadyn Ellis Building, Maindy Road, Cathays, Cardiff, CF24 4HQ trents@cardiff.ac.uk

Best C(1), Storan M(1), Moon A(1), Hall J(1)

(1) Neuroscience & Mental Health Research Institute, Hadyn Ellis Building, Maindy Road, Cathays, Cardiff, CF24 4HQ

Introduction The inhibitory neurotransmitter GABA activates postsynaptic GABAA receptors (GABAARs) and maintains inhibitory/excitatory neurotransmission. Dysregulation of GABAergic pathways have been identified in schizophrenia, autism and Fragile X Syndrome (loss of the Fmr1 gene/ FMRP protein). Indeed, preclinical Fmr1 KO models have revealed reduced GABAAR subunit expression and tonic inhibition. Intriguingly, FMRP shares similar neurobiological pathways with Cyfip1 and together they regulate synaptic protein translation. CYFIP1 represents a highly penetrant risk gene with a 2-4 fold risk for schizophrenia, and associated with autism and intellectual disability. Despite the close biological

cooperation between FMRP and Cyfip1, it is unclear if GABAergic dysfunction occurs in Cyfip1 KO models. Here we utilised a mouse and rat Cyfip1 +/- KO model to explore dysregulation of GABAergic components. For comparison, similar experiments were performed on a further genetic model (CACNA1C KO rat) and neurodevelopmental model (rodent juvenile stress) that have previously been associated with altered GABAergic signalling. Methods Brains were extracted from adult (3-4 m) male Cyfip1+/- heterozygous knockout mice (6NTac x JAX 6) and rats (Lister-Hooded, SAGE laboratories), alongside wild-type littermate controls (mice: n=12/11; rats: n=10/10). Prefrontal cortical and hippocampal regions were dissected and prepared for qPCR analysis of GABAAR synaptic subunit Gabra1, extrasynaptic Gabrd and Gabra4 and presynaptic enzyme Gad1. Primer efficiencies were verified, Gapdh and Hprt were housekeeper genes and gene expression fold change calculated via delta-delta Ct. Statistical comparisons used 1-way ANOVAs with Shapiro-Wilk normality tests. Comparison studies utilised a CACNA1C heterozygous rat (n=13/7, Sprague Dawley, SAGE Laboratories) and an early-life stress model with non-transgenic Lister-Hooded rats (3 early-life stressful events on PND25-27; brains extracted at PND60). Complementary techniques included in situ hybridisation and western blotting. Results Increased Gabrd expression was observed in the hippocampus and prefrontal cortex of Cyfip1+/- KO mice (63% and 85%, respectively; Hipp: $F(1,22)=18.554$, $P=0.0001$; PFC: $F(1,22)=5.732$, $P=0.026$). Increased Gabrd expression was similarly observed in the Cyfip1 KO rat model (PFC: 25% increase, $F(1,19)=4.746$, $P=0.043$). No further changes were observed for the remaining GABAergic components tested. Gabrd expression changes were further explored in the CACNA1C KO rat and juvenile stress model, although no changes were observed (CACNA1C KO PFC: $F(1,19)=0.892$, $P=0.357$). Conclusion Surprisingly, the expression of Gabrd, the extrasynaptic GABAAR delta subunit, was found to be increased across both rodent models of Cyfip1 deletion, but not in other genetic or early-life risk models. Gabrd may therefore play a specific role in Cyfip1 deletion that contrasts with its role in Fragile X syndrome. This work was funded by a Wellcome Trust Strategic Award (DEFINE), internal NMHRI funding and NARSAD grant (Brain & Behavior Research Foundation).

E28

GENETIC DELETION OF GPR88 RECEPTORS MODIFIES THE INFLUENCE OF AMPHETAMINE, DA AGONISTS AND PCP UPON LOCOMOTOR BEHAVIOUR IN MICE

Thomson DM, SIPBS, University of Strathclyde, Glasgow, 161 Cathedral street Glasgow, G4 0RE David.M.Thomson@strath.ac.uk

Mitchell EJ (1), Mannoury la Cour C(3), Millan MJ (3), Pratt JA(1), Morris BJ(2)

(1) As presenting author; (2) Institute of Neuroscience and Psychology, College of Medical, Veterinary and Life Sciences, University of Glasgow; (3) Servier Innovation Pole in Neuropsychiatry Suresnes, France

Introduction The orphan G protein-coupled receptor gene GPR88 is genetically associated with neuropychiatric disorders (Del Zompo et al., 2014 Mol Genet Genomic Med 2:152-159). Its neuroanatomical enrichment in medium spiny neurons suggests a potential modulation of cortico-striatal circuits and the control of locomotor function. Here we examine this potential influence of GPR88 by investigating the locomotor activity (LMA) responses of GPR88 KO mice to amphetamine and phencyclidine (PCP), and to DA receptor agonists and amphetamine following subchronic phencyclidine (scPCP) treatment. Method We used 36 male C57BL/6J wild type (WT) and 36 GPR88 KO mice, ~8-10 weeks old. Following 30min habituation, LMA was assessed for 60min in an open field (40cm x 40cm) after ip injection of saline, amphetamine (1, 2, 3mg/kg) or PCP (3mg/kg). LMA was further assessed in mice receiving amphetamine, the D1 receptor agonist SKF81297 (10mg/kg) and the D2 receptor agonist quinpirole (10mg/kg) following scPCP (10mg/kg, 2xdaily, 7 days). Movement within the arena was recorded using Ethovision. Statistical analysis used repeated measures ANOVA. Results GPR88 KO mice were hyperactive in comparison to WT mice ($F1,10 = 38.10$ $P<0.0001$). A hypersensitization to acute 2mg/kg amphetamine was observed in GPR88 KO ($F1,18 = 57.86$ $p = 0.0001$) vs WT mice. Acute PCP increased locomotor activity similarly in both genotypes ($F1,10 = 48.79$ $P<0.0001$) scPCP administration had no significant effect on basal locomotor activity in both genotypes with KO mice still being hyperactive. In WT mice, scPCP enhanced the response to 3mg/kg amphetamine ($F2,695 = 9.1$ $p<0.01$) an effect that was abolished in KO mice. In WT mice, scPCP enhanced the induction of hyperlocomotion by the D1 receptor agonist, SKF81297, and this potentiation

was absent in GPR88 KO. Conversely, in WT mice, the reduction in locomotion elicited by the D2 agonist, quinpirole, was blunted by scPCP, this effect was more pronounced in the GPR88 KO, genotype x DA agonist interaction ($F_{2,695} = 37.8$, $p<0.001$) subchronic treatment x DA agonist interaction ($F_{2,695} = 10.4$ $p<0.001$) Conclusion. Under basal conditions, GPR88 KO mice show increased spontaneous locomotor activity compared to WT mice, suggesting a potential hyper-dopaminergic phenotype, supported by hypersensitization to amphetamine Further underpinning an influence of GPR88 receptors on locomotor behaviour, its genetic deletion modified the influence of selective D1 and D2 receptor agonists following subchronic exposure to PCP. In conclusion, these data suggest a close interplay between GPR88 receptors, dopaminergic transmission and possibly glutamatergic pathways in the subcortical control of locomotor function. This research was supported by a Servier grant to the University of Glasgow and Strathclyde.

E29

SYNAPTOPHYSIN AND SYNAPTIC DENSITY IN SCHIZOPHRENIA: A META-ANALYSIS OF POST-MORTEM DATA

Osimo EF, Psychiatric Imaging Group, MRC London Institute of Medical Sciences (LMS), Robert Steiner MR Unit - Imperial College Hammersmith Campus Du Cane Road, London, W12 0NN e.osimo@gmail.com

Beck K(2), ReisMarques T(1), Howes OD(2)

(1) Institute of Psychiatry, King's College London, De Crespigny Park, London SE5 8AF; (2) Psychiatric Imaging Group, MRC London Institute of Medical Sciences (LMS), Hammersmith Campus Du Cane Road, London W12 0NN

AIMS AND HYPOTHESIS: to carry out a meta-analysis of the literature on synaptophysin levels in patients with schizophrenia and matched healthy controls. Our hypothesis was that patients with schizophrenia present lower synaptophysin levels, a measure of brain synaptic density, when compared to matched healthy controls. INTRODUCTION: schizophrenia is a complex mental disorder and its neuropathology is still debated. Post-mortem studies have suggested that synaptic loss occurs in schizophrenia, however this is still debated. Synaptophysin is a well-known surrogate marker for synaptic density and can be used as a marker of synaptic loss (Masliah et al., 1990, Journal Histochem Cytochem, 38). METHODS: the PubMed and Google Scholar databases were searched with the terms: "(Schizophrenia OR psychosis OR schizophreniform disorder)" AND "Synaptophysin" for papers published from onset of the databases until the 2nd of February 2017. We selected post-mortem case-control studies in schizophrenia quantifying synaptophysin levels in the post mortem brain. Following PRISMA guidance, the abstracts of the studies identified by the search were screened by one researcher (EFO) and the screening was independently repeated by a second author (KB) to check all potential articles were included. Inclusion criteria were: 1) original articles reporting human post-mortem data; 2) included data from cases with a diagnosis of schizophrenia determined using the Diagnostic and Statistical Manual or International Classification of Disease criteria; 3) included data from a healthy control group; 4) reported group measures for synaptophysin; 5) published in a peer-reviewed journal; 6) written in English; 7) compared synaptophysin levels among groups. Exclusion criteria were: 1) studies in patients with comorbid neurological disorders; 2) studies exclusively in animal models; 3) presented data which were not original (such as reviews); 4) used the same post-mortem material as other included studies; 5) did not provide data in a form that enabled group mean and/or variance to be determined. We took particular care in ascertaining no overlap existed between the samples used in different studies. We extracted demographic measures and synaptophysin protein density data from each of the included studies. A meta-analysis was conducted using random effect models. The main outcome measure was the difference in synaptophysin concentration in different brain areas of patients with schizophrenia and healthy controls. RESULTS: the literature search yielded 98 results, from which we identified 28 relevant papers. We only performed a meta-analysis when there were at least 4 studies in each specific brain region, thus including only 26 of the 28 studies in the quantitative synthesis. In patients with schizophrenia we found a significant reduction in synaptophysin in the hippocampus (ES: -0.65, $p < 0.01$), cingulate cortex (ES: -0.54, $p = 0.02$) and frontal cortex (ES: -0.36, $p = 0.04$) as compared to healthy controls. CONCLUSIONS: There is a reduction in synaptic density in schizophrenia in several brain areas, as assessed by synaptophysin levels. We discuss

the relevance of these findings in the context of the neurodevelopmental hypothesis of schizophrenia. Future in-vivo studies of synaptic density in schizophrenia will be required to confirm these results. No sponsorship was received for this study.

E30

IN VITRO MODULATION OF RODENT AND HUMAN NEOCORTICAL GAMMA OSCILLATIONS BY A NOVEL KV3 CHANNEL MODULATOR

Modebadze T, Institute of Neuroscience, Newcastle University, The Medical School, Framlington Place, Newcasle upon Tyne, NE2 4HH mark.cunningham@ncl.ac.uk

Gillougley C(1), Alvaro GS(2), Large CH(2), LeBeau FE(1), **Cunningham MO**(1)

(1) As presenting author; (2) Stevenage Bioscience Catalyst, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2FX, UK

Introduction: Cognitive dysfunction is a hallmark symptom of schizophrenia. Studies in patients with schizophrenia and preclinical animal models have shown that there is a disruption of synchronized high-frequency network activity and a dysfunction of parvalbumin-positive (PV+) GABAergic interneurons, both of which are critical for cognitive processing. Inhibitory fast-spiking PV+ interneurons orchestrate synchronized activity (30-80 Hz) by firing at gamma frequencies and entraining large populations of cortical pyramidal cells. The fast spiking properties and temporal fidelity of PV+ interneurons are endowed by the selective expression of Kv3.1 channels on these cells. Thus, targeting Kv3 channels, and enhancing the activity of PV+ interneurons, has potential as a pharmacological treatment for schizophrenia. Methods: Using the sub-chronic phencyclidine (PCP) rodent model, we examined a range of concentrations of a novel Kv3 modulator (AUT00206) in vitro. Prior to brain slice in vitro studies, animals were behaviourally tested (novel object recognition task) to confirm cognitive deficits in PCP treated animals versus vehicle treated rats. Kainate/carbachol induced gamma oscillations were recorded from prelimbic (PrL) and infralimbic (IL) regions of prefrontal slices obtained from both groups of animals. We also examined the effect of AUT00206 in slices of human neocortical tissue. Non-epileptic tissue was obtained during tumour debulking procedures. Gamma frequency oscillations were elicited by the bath application of kainate (400-600nM). Results: We demonstrate that higher concentrations of AUT00206 (10 and 20 μM) significantly increased the area power of gamma oscillations in PrL region in slices from PCP treated animals (10 μM: 250±59 μV2 v. 301.7±88 μV2, 21.4±8.9%, p=0.02, n=15; 20 μM: 148.6±71 μV2 v. 157.6±59 μV2, 27.2±10.2%, p=0.037, n=10). Slices from vehicle treated animals showed a significant reduction in gamma area power at 20 μM AUT00206 (209.1±99 μV2 v. 131.7±57 μV2, 29.5±7.3%, p=0.016, n=8). Similar effect of AUT00206 was observed in IL region, however only the 10 μM concentration produced a significant increase in the area power of oscillations (305.7±120 μV2 v. 380±180 μV2, 14.6±6.6%, p=0.046, n=14). In human slices the power of kainate evoked gamma oscillations was unaltered by 10 μM AUT00206 (-5.4±6.6%, n=5). In slices exposed to kainate and PCP, the power of gamma oscillations was increased by the drug (41.6±13.7%, n=8). The differential effect of AUT00206 between groups was significant (p=0.008) Conclusions: Our results suggest that modulation of Kv3 channels by AUT00206 may have the potential to correct aberrant neuronal oscillations in patients suffering from schizophrenia by augmenting gamma frequency oscillations. This work was supported by an Innovate UK/MRC Late Stage Biomedical Catalyst award.

E31

AEROBIC EXERCISE REVERSES COGNITIVE DEFICITS IN THE SUB-CHRONIC PHENCYCLIDINE RAT MODEL FOR SCHIZOPHRENIA, ROLE OF BRAIN-DERIVED NEUROTROPHIC FACTOR

Gonzalez AJ, Division of Pharmacy & Optometry and School of Biology, University of Manchester, University of Manchester, Stopford Building, 99 Oxford road, Manchester, UK, M13 9PT antoniojgonzalez195@gmail.com

Heaney LM(1), Podda G(1), Oladipo JM(1), Grayson B(1), Harte MK(1), Large C(2), Neill JC(1)

(1) As presenting author; (2) Autifony Therapeutics Ltd, Stevenage Bioscience Catalyst Incubator, Gunnels Wood Road, Stevenage, Herts.SG1 2FX, UK

Introduction: Cognitive deficits in schizophrenia remain an unmet clinical need, these have a significant impact on outcome and quality of life for patients and carers (Harvey & Keefe, 2001). The sub-chronic phencyclidine (PCP) rat model and novel object recognition (NOR) task have been well validated for relevance to schizophrenia (Neill et al., 2010; Horiguchi et al., 2012; Grayson et al., 2015). Exercise increases hippocampal and plasma levels of brain-derived neurotrophic factor (BDNF), a growth factor protein that modulates synaptic plasticity and long-term potentiation (Berchtold et al., 2005), thus providing a hypothesis for its therapeutic effects on cognitive deficit symptoms of the illness. Our aim is to investigate the mechanisms by which aerobic exercise reverses cognitive deficits in the scPCP model, with a focus on BDNF. Methods: Four groups of adult female Lister Hooded rats (n=10 per group) were used: vehicle control, vehicle exercise, scPCP control, and scPCP exercise. Rats were treated with either saline or PCP (2mg/kg i.p.) twice a day for 7 days, followed by 7 days washout then given access to running wheels in individual cages for 1 hour a day, 5 times a week, for 6 weeks. Control groups had access to immobilised running wheels. NOR tasks (with a 1 minute inter-trial interval) were conducted pre-exercise, post-exercise, 2 weeks post-exercise, and 4 weeks post-exercise. Blood samples were taken pre-exercise, post-exercise, and 8 weeks post-exercise. Plasma and brain BDNF levels were quantified by ELISA. Data were analysed by ANOVA and post-hoc student's t-test. Results: Pre-exercise vehicle, but not scPCP groups, successfully discriminated the novel from familiar object ($p<0.05$). The exercise regime reversed this cognitive deficit ($p<0.05$), while the scPCP control group remained unable to complete the task and vehicle groups successfully discriminated the novel from familiar object ($p<0.05$). The cognitive deficit reversal was sustained 2 weeks post-exercise ($p<0.05$), but the deficit returned 4 weeks post-exercise. Current work is evaluating plasma BDNF and subsequent studies will measure BDNF protein and BDNF mRNA in the hippocampus, prefrontal cortex, and frontal cortex. Conclusions: This work demonstrates that aerobic exercise therapy reverses a robust cognitive deficit in a well validated pharmacological rat model of relevance to schizophrenia. Our work to evaluate potential mechanisms of this effect through BDNF could inform future therapeutic strategies in patients. Sources of funding: This work was funded by b-neuro at the University of Manchester and Autifony Therapeutics Ltd.

E32

EFFECTS OF PHENCYCLIDINE IN SOCIAL GROUPS OF ADOLESCENT RATS MONITORED IN THE HOME CAGE

Mitchell EJ, Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, 161 Cathedral St, Glasgow, G4 0RE emma.mitchell@strath.ac.uk

Brett RR(2), Armstrong JD(1), Pratt JA(2)

(1) Actual Analytics, Appleton Tower, Edinburgh; (2) As presenting author

Social dysfunction is a core feature of several neuropsychiatric disorders including schizophrenia and autism. Rodent paradigms that measure social behaviours are crucial for elucidating the pathophysiology of social dysfunction and for predicting the efficacy of putative treatments. Currently, most social interaction paradigms are restricted to short time windows and involve removing the animal from the home cage. Here, we utilise a home cage analysis system that allows for 24 h monitoring of individual rats within established social groups. We characterise the effects of phencyclidine (PCP) on the social architecture of groups of adolescent rats. 18 male Lister-Hooded rats (5-6 wks) housed in groups of 3 were implanted with RFID transponders and the home cage was placed over a RFID baseplate for automated tracking of the location of each rat. Video recordings were overlaid with rat location data (using Actual HCA-Capture) such that individual rats could be identified during behavioural scoring. Rats were monitored for a total of 72 h (commencing at onset of the dark period). Initially, all 3 rats were injected with saline. At 24 h, a randomly selected rat received PCP (2.5 mg/kg ip). At 48 h, all 3 rats received PCP (2.5 mg/kg ip). For 1 h after each treatment condition, social interactions (pouncing, pinning, wrestling, allo-grooming, boxing, face-sniffing and ano-genital sniffing) were scored using ANVIL. Here, we present an initial analysis of the data. Analysis was performed via 1-way ANOVA. Total interaction time for PCP-treated rats towards saline-treated rats was significantly reduced relative to that of saline-treated rats towards saline-treated rats ($p = 0.05$). Examination of specific interactions showed that PCP-treated rats exhibited significantly reduced pinning of saline-treated rats compared to that of saline-treated rats

towards saline-treated rats (p = 0.03). Saline-treated animals exhibited decreased interactions towards PCP-treated animals but this effect was not significant (p values > 0.05). When the condition where all 3 rats received PCP was compared with the condition where all 3 rats received saline, there was no significant effect of PCP on total interaction time (p = 0.42); however the PCP-treated group exhibited significantly reduced ano-genital sniffing (p = 0.002), pinning (p = 0.008) and a trend towards reduced allo-grooming (p = 0.07). Thus, we have demonstrated social dysfunction in established social groups of rats within the home cage following PCP administration. This system represents a tool for elucidating neurobiological mechanisms of social dysfunction and for use in future drug discovery. Funding sources: This research was funded in part by a NC3Rs 'Rodent Big Brother' grant to Actual Analytics (JDA) and the University of Strathclyde (JAP).

E33

GPR52 IS A KEY REGULATOR OF STRIATAL SIGNALLING AND FUNCTION

Langmead CJ, Drug Discovery Biology, MIPS, Monash University, 381 Royal Parade, Parkville VIC, Australia, 3052 chris.langmead@monash.edu

Spark DL(1), Sarwar M(1), Stewart GD(1), Nithianantharajah J(2)

(1) As presenting author; (2) Florey Institute of Neuroscience & Mental Health, Royal Parade, Parkville VIC 3052, Australia

GPR52 is an orphan G protein-coupled receptor (GPCR) recently identified as a putative drug target in schizophrenia, largely based on expression in key areas of dopaminergic and glutamatergic dysregulation. GPR52 is highly expressed in the striatum, exclusively on dopamine D2 receptor-expressing medium spiny neurons (MSNs), and also on dopamine D1 receptor-expressing cortical pyramidal neurons. These represent key neuronal populations that may regulate striatal hyperdopiminergia and cortical hypodopaminergia in schizophrenia. To examine the role of GPR52 in striatal signalling, neurophysiology and striatal-dependent behaviours, we first assessed the function of the receptor using cAMP, calcium and ERK1/2 phosphorylation assays in both cells stably transfected with human GPR52 and mouse primary cultured embryonic striatal and cortical neurons with the selective synthetic agonist 3-[2-(3-chloro-5-fluorobenzyl)-1-benzothiophen-7-yl]-N-(2-methoxyethyl)benzamide (3-BTBZ). We also investigated 3-BTBZ-regulated phosphorylation of striatal signal integrator, 32kDa dopamine- and cAMP-regulated phosphoprotein (DARPP-32) by quantitative immunohistochemistry in acute mouse brain slices. Two key residues that modulate MSN excitability, threonine 34 (T34) and threonine 75 (T75) were examined in both D1- and D2 receptor-expressing MSNs. In vivo activity of 3-BTBZ (3 - 30 mg/kg, i.p.; 60 min pre-treatment time) was assessed against amphetamine (3 mg/kg, i.p.) or phencyclidine (3 mg/kg, i.p.) induced hyperactivity in mice (n = 6-7 / group) over a test period of 60 min. The effect of the compound on spontaneous motor activity was measured for 30 min prior to psychostimulant administration (30 min post 3-BTBZ dose). Time course AUC data were analysed by one-way ANOVA with Dunnett's multiple comparisons. 3-BTBZ stimulated cAMP production in both CHO-hGPR52 cells (pEC50 = 7.5 ± 0.2; n=4) and in cultured striatal neurons (pEC50 = 8.3 ± 0.2; n=4). Surprisingly, 3-BTBZ (1 μM) significantly increased T75 phosphorylation in dopamine D1-, but not D2-expressing MSNs, with no effect on T34 phosphorylation in either neuronal population. The modulatory effect on T75 phosphorylation was ablated in slices lacking cortical projection neurons, indicative of extra-striatal mediated GPR52 signalling. Systemic administration of 3-BTBZ significantly reduced amphetamine-induced hyperactivity at only 30 mg/kg (i.p.; $P<0.05$ vs. amphetamine); the same dose also significantly reduced spontaneous motor activity ($P<0.001$ vs. vehicle). However 3-BTBZ significantly inhibited phencyclidine-induced hyperactivity in mice at both 3 and 10 mg/kg (i.p.; $P<0.05$ and $P<0.01$ vs. amphetamine, respectively). These data suggests that GPR52 activation, likely via regulation of both striatal and extra-striatal cAMP signalling, modulates DARPP-32 phosphorylation and behaviour in predictive mouse models of psychosis. No sponsorship was received for this study.

E34

MIDBRAIN DOPAMINE NEURON FIRING MEDIATES THE EFFECTS OF KETAMINE TREATMENT ON LOCOMOTOR ACTIVITY: A DREADD EXPERIMENT

Kokkinou M, Medicine, MRC London Institute of Medical Sciences, Psychiatric Imaging Group, Robert Steiner MR Unit, MRC London Institute of Medical Sciences (LMS), Hammersmith Hospital, London W12 0NN, UK. Psychiatric Imaging Group, MRC London Institute of Medical Sciences (LMS), Faculty of Medicine, Imperial College London, Du Cane Road, London W12 0NN, UK., W12 0NN michelle.kokkinou08@imperial.ac.uk

Bonsall DR(3), Irvine EE(1), Ungless MA(2), Withers DJ(1), Howes OD(4)

(1) Metabolic Signalling Group, MRC London Institute of Medical Sciences (LMS), Faculty of Medicine, Imperial College London, Du Cane Road, London W12 0NN, UK.; (2) Neurophysiology Group, MRC London Institute of Medical Sciences (LMS), Faculty of Medicine, Imperial College London, Du Cane Road, London W12 0NN, UK.; (3) Psychiatric Imaging Group, Robert Steiner MR Unit, MRC London Institute of Medical Sciences (LMS), Hammersmith Hospital, London W12 0NN, UK. Psychiatric Imaging Group, MRC London Institute of Medical Sciences (LMS), Faculty of Medicine, Imperial College London, Du Cane Road, London W12 0NN, UK.; (4) Psychiatric Imaging Group, Robert Steiner MR Unit, MRC London Institute of Medical Sciences (LMS), Hammersmith Hospital, London W12 0NN, UK. Psychiatric Imaging Group, MRC London Institute of Medical Sciences (LMS), Faculty of Medicine, Imperial College London, Du Cane Road, London W12 0NN, UK. Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, Kings College London, London, UK

Introduction: Ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, has demonstrated rapid and sustained antidepressant effects in patients with treatment-resistant depression, yet its use is limited due to dissociative, psychotomimetic and cognitive side-effects associated with the doses used for treatment (Berman et al., 2000, Biological Psychiatry, 47, 351-354; Stone et al., 2014, Psychopharmacology, 231, 2107-2116). Sub-anaesthetic doses of ketamine in healthy human subjects induce symptoms comparable to symptoms of schizophrenia (Krystal et al., 1994, Archives of general Psychiatry, 51, 199-214) and suggest that ketamine-induced effects in experimental animals could serve as pharmacological models of schizophrenia. In addition elevated dopamine synthesis and release are seen in people at risk of developing schizophrenia (Howes et al., 2009, Archives of general psychiatry 66, 13-20). Our aim was to investigate whether sub-chronic ketamine-induced hyperactivity in the male mouse involved the dopaminergic system. Specifically we tested the role of midbrain dopamine neuron firing in mediating the ketamine-induced hyperactivity. Methods: Twenty-eight mice received a sub-anaesthetic dose of ketamine or saline for five consecutive days and locomotor activity was assessed in the open field test. Dopamine neurons in ventral tegmental area (VTA) and substantia nigra pars compacta (SNc) specifically were transduced with an adeno-associated virus vector expressing Gi-coupled (hM4Di) DREADDs (designer receptor exclusively activated by designed drug) under control of Dat promoter in a separate cohort of forty-three Dat Cre positive mice. Standard immunohistochemistry was used to label dopamine neurons and reporter expression was confirmed using confocal microscopy. Two weeks following the stereotaxic injection of the viral construct, mice were pre-treated with clozapine N-oxide (CNO) to selectively inhibit dopamine neuron firing or saline to investigate the effect on locomotor activity in the sub-chronic ketamine model. Data were analysed by two-way ANOVA followed by Bonferroni post hoc tests and $p<0.05$ was considered statistically significant. Results: Acute and sub-chronic ketamine treatment significantly increased locomotor activity compared to saline treated controls ($p<0.01$). Moreover sub-chronic ketamine treatment induced locomotor sensitization ($p<0.01$). Co-expression of mCherry and TH confirmed expression of the hM4Di DREADDs in the VTA and SNc dopamine neurons. Ketamine's effects on locomotor activity were reversed by DREADD-mediated inhibition of midbrain dopamine neuron firing prior to ketamine administration ($p<0.01$). Conclusion: Our data indicate ketamine's effects on locomotor activity required midbrain dopamine neuronal activity. This finding provides new evidence explaining the psychotomimetic effects of ketamine reinforcing the utility of the sub-chronic ketamine model for preclinical investigations of dopaminergic overactivity in schizophrenia. This study was funded by a Medical Research Council (UK) grant to Professor Howes (Grant no. MC-A656-5QD30).

E35

OXYTOCIN ENHANCES PRO-SOCIAL BEHAVIOUR, ATTENUATES PCP-INDUCED HYPERACTIVITY AND INCREASES DOPAMINE OVERFLOW IN THE NUCLEUS ACCUMBENS IN THE RAT

Kohli S, SoLS, Uni of Nottingham, Uni of Nottingham Medical School QMC Nottingham, NG7 2UH mbxsk2@nottingham.ac.uk

Edwards A(1), Alberati D(2), Ballard TM(2), Steward LJ(2), King MV(1), Fone KCF(1)

(1) As presenting author; (2) Neuroscience, Ophthalmology & Rare Diseases, Roche Pharma Research & Early Development, Roche Innovation Center, Basel, Switzerland

The pituitary neuropeptide oxytocin modulates social behaviours and shows potential as an adjunct therapeutic for disorders manifesting social deficits such as schizophrenia or autism. However, the precise mechanisms by which oxytocin influences rat behaviour are relatively unknown. As oxytocin has affinity for vasopressin V1A receptors, which results in accompanying cardiovascular and thermoregulatory effects, this study attempted to identify a dose of oxytocin that affected social behaviour without confounding effects on body temperature. Group-housed adult male Lister-hooded rats (175-200g, Charles River UK) were implanted with subcutaneous (s.c.) temperature microchips (Bio-Therma iDENTICHIP; AnimalCare Ltd) to record body temperature during behaviour. Following 30min habituation, rats (n=12) received oxytocin (0.03, 0.1 or 0.3mg/kg s.c.) or saline (1ml/kg) in a random cross-over design across four weeks (7d intervals) and locomotor activity (LMA) was recorded for 2h. A separate group of rats (n=32) received oxytocin (0.1mg/kg s.c.) or saline (1ml/kg) during all behavioural tests. During LMA, after the first injection with oxytocin or saline, rats received phencyclidine (PCP; 5.6mg/kg i.p.) or saline (2ml/kg) 25min later. Vehicle-treated rats were then matched for weight and treatment to examine the effects of acute oxytocin on social interaction and ultrasonic vocalisations (USVs; 10min trial 7d after LMA), and monoamine release in the prefrontal cortex (PFC) and nucleus accumbens (NAc) was measured using microdialysis in freely-moving rats (n=16 14d after LMA). Oxytocin at the highest dose (0.3mg/kg, but not 0.03-0.1mg/kg) induced hypothermia ($p=0.001$; two-way RM-ANOVA) without influencing LMA. A lower dose of 0.1mg/kg had no significant effect on core body temperature and significantly attenuated PCP-induced hyperactivity in an open field ($p<0.01$; Tukey post-hoc). Additionally, 0.1mg/kg oxytocin increased social interaction (specifically ano-genital and body sniffing; $p=0.0008$ and $p=0.0610$ respectively; Sidak post-hoc), without concomitantly altering the number of USVs. In the same rats, oxytocin (0.1mg/kg) selectively elevated dopamine levels in the NAc but not PFC ($p=0.0153$; two-way RM-ANOVA) and did not alter serotonin overflow in either region. Peripherally administered oxytocin enhanced pro-social behaviour and attenuated PCP-induced hyperactivity without producing concomitant thermoregulatory side-effects in rats. The selective increase in NAc dopamine overflow suggest oxytocin-dopamine interactions occurring in the mesolimbic dopamine pathway might contribute to the pro-social behavioural effects produced by oxytocin. Together these results highlight that oxytocin may have potential value as an adjunct therapeutic to treat negative symptoms as well as residual, likely not dopamine driven positive symptoms of schizophrenia, and other psychiatric disorders involving altered glutamatergic and dopaminergic neurotransmission. Funded by F. Hoffmann-La Roche Ltd.

E36

GESTATIONAL POLY(I:C) ATTENUATES FRONTAL CORTICAL CYTOKINE, MTOR AND SEROTONERGIC RESPONSES TO ISOLATION REARING IN A 'DUAL-HIT' MODEL FOR SCHIZOPHRENIA

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

Shortall SE(1), Goh J-Y(1), O'Sullivan SE(2), Bushby K(1), Herbert EA(1), Ravat F(1), Shotton L(1), Fone KCF(1)

(1) As presenting author; (2) School of Medicine, University of Nottingham, Royal Derby Hospital, Derby DE22 3DT

Maternal infection and early-life social adversity are risks for schizophrenia. We previously combined gestational polyinosinic:polycytidylic acid (poly(I:C), via the i.p. route) with post-weaning isolation rearing as a potential 'dual-hit' rat neurodevelopmental model for schizophrenia, and found the viral mimetic actually attenuated components of the isolation-induced behavioural syndrome (Goh et al. 2016

J. Psychopharmacol. 30S:A36). This study extends these findings by investigating attentional set shifting and underlying cytokine, mTOR signalling and neurotransmitter alterations. Seventeen Lister-hooded dams (CRUK, 280-337g) received saline (1ml/kg i.p.; Veh) or 10mg/kg poly(I:C) on GD15. Male pups (n=96) were housed in groups (4/cage; Gr) or individually (Iso) from weaning (post-natal day 22). Brain samples were collected for immunohistochemical analysis of frontal cortical 5-HT and SERT after attentional set shifting (9-15w post-weaning) or GABAergic interneurons and reelin in the dorsal hippocampus after alternative cognitive tests (10w post-weaning). Frontal cortical and hippocampal cytokines and mTOR were quantified by multiplex assay (2 and 10w post-weaning). Data (n=8 per treatment/housing/age) were analysed by 2/3-way repeated measures ANOVA with Sidak's post-hoc. Overall rats found reversal 1 and the extradimensional shift harder than compound discrimination and the intradimensional shift. Veh-Iso exhibited a selective impairment in reversal 1 (16±3 trials to criterion whereas Veh-Gr 9±1; $P<0.05$), accompanied by reduced orbitofrontal (but not prelimbic) 5-HT:SERT ratio ($P<0.05$ versus Veh-Gr). There were main effects of housing on parvalbumin ($F(1,28)=4.499$, $P=0.0429$) and calbindin ($F(1,28)=4.875$, $P=0.0356$) positive interneurons in CA2/3, although neither decrease reached post-hoc significance. At the same time Veh-Iso had elevated frontal cortical cytokines (IL-1β, IL-2, IL-6, IL-10, IL-12 and TNFα; $P<0.05$-0.01 versus Veh-Gr) and p-mTOR:mTOR ($P<0.0001$ versus Veh-Gr) not seen in poly(I:C)-Iso ($P>0.05$ versus Veh-Gr; IL-10/IL-12 $P<0.05$ and p-mTOR:mTOR $P<0.0001$ versus Veh-Iso). None of these changes were apparent 2w post-weaning after onset of locomotor hyperactivity but prior to assessment (and predicted onset) of cognitive and social deficits. Gestational exposure to a viral mimetic (by i.p. injection that induced maternal sickness behaviour and weight loss) attenuated frontal cortical responses to isolation rearing, supporting an inoculation rather than cumulative stress hypothesis. However, contrasting findings submitted to this meeting reveal that 6mg/kg poly(I:C) via the i.v. route exacerbates isolation-induced behavioural deficits (Goh et al. 2017), with cytokine/mTOR analyses in progress. We did not detect cytokine/mTOR alterations preceding cognitive/serotonergic dysfunction in this study, but future research will investigate this temporal relationship in more detail and explore opportunities for early therapeutic intervention. Funded by The University of Nottingham and Monash University.

E37

PREBIOTIC INTAKE ATTENUATES OLANZAPINE-MEDIATED WEIGHT GAIN IN RATS WITHOUT COMPROMISING CENTRAL EFFECTS

Kao A, Psychiatry, University of Oxford, Neuroscience Building Warneford Hospital Warneford Lane Oxford, OX3 7JX amy.kao@psych.ox.ac.uk

Lennox B(1), Burnet PW(1)

(1) As presenting author

Introduction: Olanzapine (OLZ) is an effective antipsychotic medication for schizophrenia, but has limited effects on cognitive deficits and often causes severe weight gain leading to secondary health concerns. Studies in rats suggest that reduced cortical serotonin receptor 2A (5-HT2A) following OLZ administration may underlie its antipsychotic properties. However, decreased hippocampal glutamate N-methyl-D-Aspartate receptors (NMDAR) has also been associated with OLZ administration, which may hinder the recovery of cognitive function in schizophrenia patients. We have shown that dietary augmentation of beneficial gut bacteria using the prebiotic Bimuno® galacto-oligosaccharides (B-GOS) increases central levels of NMDAR subunits in rodents. The aim of this study was to determine whether the effects of OLZ on weight gain and central receptor levels in rats are influenced by B-GOS intake. Methods: Adult female Sprague-Dawley (n = 24) rats were provided with drinking water supplemented with B-GOS (0.5g/day) or normal drinking water for 7 days, before receiving a single injection of OLZ (10mg/kg/day; i.p.) or saline, for 14 days. B-GOS supplementation continued for the duration of OLZ administration. Weight gain and water intake were monitored daily. The levels of NMDAR subunit (GluN1, GluN2A, GluN2B) and serotonin receptor (5-HT1A, 5-HT2A) proteins and mRNAs were measured in the frontal cortex and hippocampus. Two-way ANOVAs were used to analyse all data, with repeated measures included to explore weight gain. Results: OLZ conferred significant weight gain ($p < 0.001$) compared to saline-controls, which was not observed in OLZ-injected animals on the B-GOS diet. Although a B-GOS x OLZ interaction was not observed for central NMDAR subunit levels, OLZ administration overall, increased cortical GluN1 ($p = 0.002$) and

GluN2A (p = 0.036) mRNAs. This was driven by the significant increase (16%) between B-GOS/saline and B-GOS/OLZ groups (p = 0.003). Cortical 5-HT2A, but not 5-HT1A, protein levels were significantly reduced (p < 0.001) by OLZ. Conclusions: Our data indicate that prebiotic B-GOS intake attenuates OLZ-induced weight gain without altering central 5-HT2AR blockade which has been associated with the clinical action of this antipsychotic. Moreover, this study has shown that OLZ elevates NMDAR subunits in the frontal cortex of female rats, which may be potentiated by B-GOS. Previous work has only demonstrated reduced hippocampal NMDARs by OLZ in male rats, where anti-psychotic induced weight gain is not observed. These data suggest that inclusion of B-GOS as an adjunct to OLZ treatment in schizophrenia may have benefits on cognitive function, as well as preventing weight gain. Financial Disclosure : Clarendon Fund, University of Oxford.

E38

NEUREXIN-1 HYPOFUNCTION EXTENDS LIFE SPAN, AMELIORATES BEHAVIOURAL SENESCENCE AND ALTERS SLEEP STRUCTURE IN DROSOPHILA MELANOGASTER

Hughes RB, BLS, Lancaster University, Lancaster, LA1 4YQ r.hughes7@lancaster.ac.uk

Broughton S(1), Dawson N(1)

(1) As presenting author

Introduction: Schizophrenia is associated with early death and may involve accelerated ageing. A number of Schizophrenia risk genes have been identified, including deletions in Neurexin-1. Whether these genetic risk factors accelerate ageing is yet to be determined. Methods: We utilised a Neurexin-1 (Nrx-1) hypomorph Drosophila model (P {XP} Nrx-1d08766) in both an inbred (white1118) and an outbred (whiteDahomey) genetic background to investigate how Neurexin-1 hypofunction affects life span, locomotor behaviour (open field) and sleep across the life span. To study life span dead and censored flies were recorded 3-5 times a week. Open field and sleep analysis were performed at weekly intervals from 11-53 days old. Locomotor activity in a novel circular arena was recorded for 15 minutes and analysed using Ethovision XT. For sleep analysis flies were placed into the Drosophila Activity Monitoring System (DAMS) for 4 days. Sleep data was analysed using BeFly! Analysis tools v7.23. For open field and sleep analysis n=16 per group per time point. For the life span study n=100 per group. Differences in median life span were statistically analysed using the log-rank test. ANOVAs were used to analyse locomotor and sleep data to determine the effects of genotype, age, genetic background and sex. Interactions were analysed using post-hoc Tukey's HSD. Significance was set at $p<0.05$. Results: Neurexin-1 hypofunction significantly extended life span in flies with an outbred genetic background (chi-squared, $P<0.0001$). As flies aged they spent significantly more time in the central zone of the open field arena ($P<0.0001$, ANOVA). This effect was significantly attenuated in Neurexin-1 hypomorph flies ($P<0.01$ genotype x age interaction; control versus Nrx-1 hypomorph, $P<0.05$ at 46 and 53 days old). Alongside age-related effects Neurexin-1 hypofunction caused significant hyperactivity (increased walking distance and velocity) in male but not in female flies ($P<0.01$ genotype x sex; male controls vs male Nrx-1 hypomorphs $P<0.001$) and altered sleep structure, significantly decreasing the number of sleep bouts ($P<0.0001$ genotype x sex; female controls vs female Nrx-1 hypomorph $P<0.001$), in female but not male flies. Conclusions: In contrast to our expectation that Neurexin-1 hypofunction would shorten life span, it extended lifespan and ameliorated locomotor behavioural senescence. In addition to age related effects Neurexin-1 hypofunction caused hyperactivity and altered sleep structure in a sex-dependent manner. These studies highlight the utility of Drosophila as a model organism for studying the impact of psychiatric risk genes on lifespan and behavioural senescence. Financial Support: This work was supported by Lancaster University.

E39

HAPLOINSUFFICIENCY OF SCHIZOPHRENIA RISK GENE CYFIP1 INCREASES ADULT HIPPOCAMPAL NEUROGENESIS THROUGH INCREASED NEURONAL SURVIVAL

Haan N, NMHRI, Cardiff University, Neuroscience and Mental Health Research Institute, College of Biomedical & Life Sciences, Cardiff University Hadyn Ellis Building, Maindy Road, Cardiff, CF24 4HQ, UK, CF24 4HQ haann@cardiff.ac.uk

Westacott L(1), Carter J(1), Hall J(1), Wilkinson L(1)

(1) NMHRI, Cardiff University, Cardiff, CF24 4HQ

Introduction Large scale genomic screenings have identified many genetic risk factors for schizophrenia. One of these is the 15q11.2 BP1-BP2 deletion. Four genes are located in this genomic region, including cytoplasmic FMR1 interacting protein 1 (CYFIP1). CYFIP1 can regulate both mRNA transcription and cytoskeletal remodelling through different interaction partners, and has been shown to be involved in regulation of dendritic morphology and synaptic protein translation. Adult hippocampal neurogenesis (AHN), the formation of new neurons in the granular layer of the dentate gyrus, is a complex, multi-step process. Newly born neurons are preferentially involved in a number of behaviours, including pattern separation, forgetting and anxiety. Post-mortem studies have suggested disrupted AHN in schizophrenia patients, and many of the processes AHN supports are implicated in schizophrenia symptoms. However, the links between genetic risk factors and AHN are still largely unstudied. Methods In this study, we used a heterozygous knockout mouse model to study the role of CYFIP1 in AHN. A combination of immunohistochemistry for neurogenesis markers and primary hippocampal progenitor cultures was used to assess the impact of CYFIP1 haploinsufficiency. Results Immunohistochemistry and quantification of the newborn neuron marker DCX revealed a significant ($p<0.001$) increase in the Cyfip1+/- animals (n=8 each). There was no difference in the number of proliferative cells (Ki67+) or the population of dividing cells (BrdU incorporation). Primary cultures confirmed the absence of an effect of CYFIP1 haploinsufficiency on cell proliferation, and further showed no differences in numbers of early or intermediate progenitor cell types (n=12 each). During normal AHN, many of the newly born neurons (>50%) die during maturation. Without a difference in progenitor cell numbers and proliferation rates, increased survival is a likely explanation for increased number of new neurons. Indeed, Cyfip1+/- primary cultures showed higher numbers of viable cells ($p<0.01$) and lower number of dead cells ($p<0.05$) than wild type controls (n= 6 and 11, respectively). Conclusions Our findings show that haploinsufficiency of CYFIP1 increases adult hippocampal neurogenesis through improving survival of newly born neurons. This work represents the first evidence of a link between Cyfip1 and hippocampal neurogenesis. Further work on the mechanistic links between Cyfip1 and cell survival and on the behavioural consequences of increased neurogenesis is ongoing. The effects of Cyfip1 and other schizophrenia risk genes have on AHN suggest it represents a potentially important aspect of disease pathophysiology. This work was funded by a Wellcome Trust Strategic Award (DEFINE).

E40

COGNITIVE AND SOCIAL BEHAVIOUR DEFICITS AT ADULTHOOD IN FEMALE RAT OFFSPRING OF POLY I:C TREATED RAT DAMS, A DEVELOPMENTAL MODEL FOR SCHIZOPHRENIA

Grayson B, Division of Pharmacy and Optometry, University of Manchester, b-neuro Stopford Building 2.019g Oxford Road Manchester, M13 9PT ben.grayson@manchester.ac.uk

Fasolino V(1), Edye M(1), Oladipo J(1), Idris N(1), Harte MK(1), Neill JC(1)

(1) As presenting author

Background Maternal immune activation (mIA) by administration of the viral-mimetic polyriboinosinic-polyribocytidylic acid (polyI:C) is a key model for neurodevelopmental disorders (NDDs) such as schizophrenia (Knuesel et al, 2014. Nat Rev Neurol, 10: 643-660). We have established that the most robust systemic inflammatory response to poly-I:C is produced by an acute dose of 10 mg/kg i.p. in rats of the Wistar strain. Our aim here is to investigate the behavioural consequences of mIA in male and female offspring at specific developmental time points. Method Pregnant female Wistar rats were injected intraperitoneally (i.p) with poly I:C (10 mg/kg, n=6) or saline (0.9% NaCl, n=5) at gestational day

(GD) 15, (10-weeks old). The offspring were tested at adolescence (postnatal day-PND-35-41) on the open field (OF) and elevated plus maze tests (EVPM) for anxiety, for social interaction (SI), and novel object recognition (NOR) for short term recognition memory and again at adulthood (PND 65-68) in SI, NOR and EVPM. Female adults only were tested between PND100-110 in the attentional set-shifting task (ASST) for executive function. Data are expressed as the mean ± SEM (n=7-10) and analysed using ANOVA and /or Student's t-test. Results 10 mg/kg poly I:C at GD15 significantly increased IL-6 3h post-injection ($P<0.05$). No significant behavioural effects of poly-I:C were observed in either sex at adolescence. However, when the same rats were tested at adulthood, the vehicle treated female offspring spent significantly ($P<0.01$) more time exploring the novel compared to familiar object, whereas the poly-I:C offspring explored both objects equally in NOR and in SI they showed reduced sniffing ($p=0.056$) and following ($p=0.12$) effects however that failed to achieve statistical significance. In the same cohort, a significant impairment in ASST was observed in female poly I:C offspring, with a significant increase in trials to criterion ($P<0.001$). No significant effects of poly-I:C were seen on EVPM and OF at any time point, in either sex. Futhermore, no significant effects were seen in NOR or SI in the adult male Poly-I:C rats. Conclusion We have established a robust model of mIA in Wistar rats and used this to identify the longitudinal development of behavioural changes. Poly-I:C at GD15 induced an immune response in Wistar rats, at a dose of 10 mg/kg i.p. Behavioural deficits were not detectable during adolescence, but these social behaviour deficits seemed to be emerging and a cognitive deficit phenotype was observed in adulthood in females. The neurobiological mechanisms for these behavioural effects are currently being investigated. Sources of financial sponsorship: This work was supported by a studentship funded by the Division of Development & Alumni Relations and the Faculty of Biology, Medicine and Health awarded to Victoria Fasolino at UoM, and by b-neuro and The Rosetrees Trust.

E41

MATERNAL POLY(I:C) INJECTION FOLLOWED BY POST-WEANING ISOLATION REARING OF RATS: OPTIMISATION OF A NOVEL 'DUAL-HIT' NEURODEVELOPMENTAL MODEL FOR SCHIZOPHRENIA

Goh J-Y, School of Life Sciences, The University of Nottingham, University of Nottingham Medical School, QMC, Nottingham, NG7 2UH mbxjg1@nottingham.ac.uk

Fone KCF(1), King MV(1)

(1) As presenting author

Gestational viral infection and early-life social adversity are recognised risk factors for schizophrenia. Administration of the viral mimetic polyinosinic:polycytidylic acid (poly(I:C)) and post-weaning isolation rearing have both independently been used as rat neurodevelopmental models to replicate symptoms associated with mental disorders. This study evaluated if i.v. poly(I:C) followed by post-weaning isolation rearing (Iso) resulted in more robust replication of such symptoms compared to i.p. poly(I:C)+Iso (Goh et al., 2016, J.Psychopharmacol., 30S, A36). Fifteen Lister-hooded dams (CRUK, 251-316g) received temperature microchips (s.c.) on gestational day (GD) 14 and i.v. saline (1ml/kg, Veh) or poly(I:C) (6mg/kg) on GD15 and sickness behaviour was monitored for 3d. Male pups (n=78; n=18-20/combination) were housed in groups (3-4/cage; Gr) or Iso from weaning (post-natal day 22). Rats underwent consecutive assessment of locomotor activity in a novel cage (LMA), novel object/location discrimination (NOD/NOL), social interaction and pre-pulse inhibition of acoustic startle (PPI) at one-week intervals commencing five weeks post-weaning, followed by either associative learning, conditioned freezing response (CFR, n=10/combination), or bowl digging attentional set-shifting (n=8-10/combination). Data (mean±SEM) were analysed by 2-way ANOVA with Sidak/Tukey post-hoc. Poly(I:C)-treated dams showed hypothermia 2h (-0.8±0.3°C, $p<0.05$) and weight loss 24h post-injection ($p<0.01$ versus vehicle). During LMA there were main effects of housing and poly(I:C) treatment; poly(I:C)-Iso offspring being more active than all other groups, but there were no impairments in NOD/NOL or PPI irrespective of housing/treatment. In CFR, both poly(I:C)-Iso and Veh-Iso rats froze for less time during acquisition of the task (poly(I:C)-Iso, $p<0.05$, first and second foot shocks; Veh-Iso, $p<0.05$, second and third shocks). At 24h on return to the conditioning chamber, there were main effects of housing and treatment on freezing duration but the small reduction freezing in both Iso groups was not significant from their same treatment Gr control. On re-exposure to the light and tone cue previously paired with foot shock, Veh-Iso froze significantly less (40±2s, $p<0.05$) than

other groups (Veh-Gr=52±1s, poly(I:C)-Gr=49±2s, poly(I:C)-Iso =43±4s). In attentional set-shifting all groups found the extradimensional (ED) harder than the intradimensional (ID) shift but only poly(I:C)-Iso rats made significantly more ED than ID errors ($p<0.05$). Gestational poly(I:C) exposure produced paradigm-specific alterations in the subsequent response to Iso, suggesting maternal immune activation can confer both susceptibility (LMA) or resilience (CFR) to an additional stressor. Brain cytokine and mTOR analyses are in progress in an attempt to identify molecular mechanisms underlying this neurodevelopmental interaction. Funded by The University of Nottingham and Monash University.

E42

TRANSLATIONAL ALTERATIONS IN GENE EXPRESSION OF GABAERGIC MARKERS IN SCHIZOPHRENIA AND IN RATS UNDERGOING ISOLATION REARING FROM WEANING

Fachim HA, Department of Neuroscience and Science of Behavior, Ribeirão Preto Medical School, University of São Paulo, Av Bandeirantes, 3900, 14048900 hfachim@yahoo.com.br

Loureiro CM(3), Corsi-Zuelli FMG(1), Louzada- Junior P(3), Menezes PR(5), Joca SR(4), Reynolds GP(2), Shuhama R(1), Del-Ben CM(1)

(1) As presenting author; (2) Biomolecular Research Centre, Sheffield Hallam University, UK.; (3) Department of Internal Medicine, Division of Clinical Immunology. Ribeirão Preto Medical School, University of São Paulo, Brazil.; (4) Department of Physics and Chemistry, School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, Brazil.; (5) Department of Preventive Medicine. Faculty of Medicine, University of São Paulo, Brazil

Introduction: GABAergic neurotransmission is affected in schizophrenia (Zhang and Reynolds, 2002. Schizophr Res 55:1–10) and among the abnormalities there are decreases in reelin, parvalbumin (Pvalb) and GAD67) (Reynolds et al., 2001. Brain Res Bull 55:579–584). These changes have been found in both postmortem human brain and in animal models of the disease. However, it is not known if there are equivalent mRNA changes in rats reared in isolation or in blood of patients in early stage of schizophrenia. The aim of this study was to evaluate the translational alterations in gene expression of reelin, Pvalb and GAD1, in both peripheral blood samples of patients after their first episode of psychosis, and in brain tissue of rats reared in isolation. Methods: Male Wistar rats (n = 10 / group) were housed isolated or in groups (n = 2/3 per cage) from weaning for 10 weeks. They were exposed to the open field and soon afterwards sacrificed; hippocampus and prefrontal cortex (PFC) were dissected prior to RNA extraction. Human blood samples (HBS) were collected from patients after their first episode (n = 26), from siblings (n = 10) and from population-based controls (n = 17). Q-PCR was performed using probes and TaqMan mastermix. T test was used for statistical analysis of animal studies, and Kruskal-Wallis as general test and Mann-Whitney as pairwise test for human studies. Results: Isolation-reared animals demonstrated hyperlocomotion at the first time bin in open field when compared to group-housed animals ($t = 1.\ 473$; $p = 0.024$). Relatively decreased expression of Pvalb (64%) and GAD1 (57%) were found in PFC of isolated animals ($t = 2.391$; $p = 0.02$); ($t = 2.083$; $p = 0.05$), while no differences were found in the hippocampus of these animals for both genes. No differences were found in reelin expression in any studied areas. Reduced Pvalb (36%) was found in HBS of male patients compared to male controls ($\chi 2 = 7.6$; $p = 0.023$), while no differences were found within the female group. No differences were found in reelin expression in HBS while GAD1 was not expressed in these samples. Conclusion: The animal data reinforce the validity of the isolation model and emphasize the hypofrontality features of the disease. Furthermore, this is the first study showing reduced Pvalb expression in HBS of schizophrenia male patients, extending the brain alterations to the periphery and highlighting the typical sex differences present in the disease. Financial Support: FAPESP.

E43

ELECTROPHYSIOLOGICAL PROPERTIES OF THE HIPPOCAMPUS-MEDIAL PREFRONTAL CORTEX PATHWAY IN THE SUB-CHRONIC PHENCYCLIDINE MODEL FOR SCHIZOPHRENIA

Doostdar N, Division of Pharmacy and Optometry, The University of Manchester, Stopford Building, Oxford Road, Manchester, M13 9PT nazanin.doostdar@postgrad.manchester.ac.uk

Davy O(2), Neill JC(1), Gigg J(2)

(1) As presenting author; (2) Division of Neuroscience and Experimental Psychology, Stopford Building, Oxford Road,M13 9PT

Introduction The functional coupling between the ventral hippocampus (VH) and medial prefrontal cortex (mPFC) is integral to context-dependent memory retrieval and goal directed behaviour. Disruption to VH-mPFC in schizophrenia (SZ) is thought to be responsible for deficits in these cognitive processes (Godsil et al., 2013, Eur Neuropsychopharm 23, 1165–1181). However, the underlying mechanisms for this remain relatively unexplored. This study addresses this by assessing synaptic plasticity and functional connectivity between VH-mPFC in the sub-chronic phencyclidine (scPCP) model of neurocognitive deficits in SZ. Methods 27 Adult female Lister-Hooded rats were randomly assigned to receive intraperitoneal (i.P) treatment with PCP-HCl (2 mg/kg, n=15) or vehicle (0.9% saline, n=12) twice daily for 7 days, followed by 7 days of washout. Performance in the novel object recognition test was assessed twice, once before the start of the electrophysiological work and once half way through, in a sub-set of rats, to confirm persistence of the deficit. Electrophysiological recordings were obtained under urethane anaesthesia (30% w/v, 1.5 g/kg, i.p). VH-evoked mPFC responses were recorded (2x16 MEA, Neuronexus Tech., USA) to assess functional connectivity (20 pairs, 100-800uA current intensity), short-term (20 pairs, 25-1000 ms interpulse interval) and long-term synaptic plasticity (LTP: 200Hz burst of 20 pulses, 5 repeats) and depotentiation (900 pairs, 1Hz). Data were analysed using one/two-way-ANOVA followed by LSD/Bonferroni post-hoc analysis when required. Results The vehicle-treated rats explored the novel object significantly more than the familiar at both time-points ($P<0.05$). This ability was lost in the scPCP-treated rats when first tested ($p=0.38$) and at the second time-point ($p=0.056$). Analysis of the slope and amplitude of the Input/Output and paired-pulses responses revealed no significant difference between the treatment groups. The VH-mPFC pathway retained its ability to undergo LTP in both treatment groups. The stability of LTP in scPCP-treated rats was much more sensitive to low-frequency stimulation (LFS) patterns used to induce depotentiation. In this treatment group LFS completely reversed the LTP to values below the baseline suggesting a long-term depression-like effect. Conclusion We have repeatedly shown robust cognitive and pathological deficits of relevance to SZ in the scPCP model. Outcome of this study suggests that synaptic connectivity and short-term plasticity remains intact in scPCP-treated rats. The instability of LTP observed in the scPCP-treated rats may explain some of the cognitive deficits associated with SZ. Further investigation is warranted to characterise the behavioural ramifications of this finding in our scPCP model. This work was funded by the President's Doctoral Scholar's Award and by the b-neuro laboratory associated with the University of Manchester.

E44

LOCOMOTOR DEFICITS IN A 16P11.2 DUPLICATION MOUSE MODEL ARE REVERSED BY MINOCYCLINE

Bristow GC, Division of Biomedical and Life Sciences, University of Lancaster, Bailrigg, Lancaster, LA1 4YW g.bristow@lancaster.ac.uk

Thomson DM(3), Pratt JA(3), Morris BJ(2), Dawson N(1)

(1) As presenting author; (2) Institute of Neuroscience and Psychology, Univ. of Glasgow; (3) Strathclyde Institute of Pharmacy & Biomedical Sciences, Univ. of Strathclyde

Introduction: Copy number variations are implicated in the etiology of psychiatric disorders. Duplication at 16p11.2, affecting approximately 30 genes, increases the risk of developing schizophrenia (Psychiatric Genomics Consortium, 2017. Nat Genet 49: 27). The antibiotic minocycline has been shown to improve cognitive and negative symptoms in patients with schizophrenia (Chaudhry et al. 2012. J Psychopharmacol. 26:1185; Solmi et al. 2017. CNS Spectr. 9:1). Here we test the ability of minocycline to reverse behavioural deficits in a mouse model of 16p11.2 duplication (DUP mice, Horev G et al. 2011. PNAS. 108: 17076).

Methods: We measured locomotor activity in the open field of 10 DUP and 10 wild-type littermate control mice (all male) before and after minocycline treatment. Activity was recorded in a circular arena for 15 minutes. Minocycline (69.12±1.88 mg/kg/day) was administered in drinking water for 6 days. Data were analysed using repeated measures ANOVA with post-hoc Tukey's HSD. Results: Drug naïve DUP mice showed significantly lower activity compared to controls (distance travelled p=0.026; time spent moving p=0.044; velocity p=0.020). By contrast DUP mice spent a similar amount of time in the central zone of the arena (p=0.999), suggesting that their activity deficit was not related to anxiety. Following minocycline treatment there was no significant difference in activity between the genotypes (distance travelled p=0.997; time moving p=0.999; velocity p=0.999). Discussion: This is the first report of the effects of minocycline in a mouse model of the 16p11.2 CNV. Our data confirm previous reports of decreased locomotor activity in 16p11.2 DUP mice (Horev et al. 2011; Arbogast et al. 2016. PLoS Genet. 12: e1005709), and extend this to show that this deficit can be corrected pharmacologically. Our data further support the potential efficacy of minocycline in the treatment of psychiatric disorders. Further research is required to determine the mechanisms through which minocycline alters behaviour in this model and whether the other behavioral deficits seen in DUP mice can be reversed with minocycline treatment. This research was funded through an MRC award to ND, JP, and BM.

F01

COMPARISON OF RESTING-STATE FMRI DATA FROM MULTIPLE DRUG STUDIES USING MULTI-VOXEL PATT1ERN ANALYSIS: STRIATAL NETWORKS

Kowalczyk OS, Centre for Neuroimaging Sciences, Institute of Psychiatry, De Crespigny Park London, SE5 8AF olivia.kowalczyk@kcl.ac.uk

Gall A(5), Verneuil T(6), Demetriou L(6), Roseman L(2), de Simoni S(4), Nutt DJ(2), Curran HV(3), Mehta MA(1), Carhart-Harris R(3), Wall MB(6)

(1) As presenting author; (2) Centre for Neuropsychopharmacology, Division of Brain Sciences, Faculty of Medicine, Imperial College London, London W12, UK ; (3) Clinical Psychopharmacology Unit, Research Department of Clinical, Educational and Health Psychology, University College London, Gower St, London, WC1E 6BT; (4) Computational, Cognitive and Clinical Neuroimaging Lab (C3NL), Division of Brain Sciences, Faculty of Medicine, Imperial College London, London W12, UK; (5) Department of Psychology, Royal Holloway University of London, Egham, Surrey, TW20 0EX; (6) Imanova Centre for Imaging Sciences, Burlington Danes Building, Imperial College London, Hammersmith Hospital, Du Cane Road, London, W12 0NN

Introduction Resting-state functional Magnetic Resonance Imaging (rs-fMRI) enables comparisons to be made across multiple studies. This is because of its relatively standardised methodological parameters and the universality of its underlying brain processes (Biswal et al., 2010, PNAS, 107(10),4734-9). Pharmacological fMRI studies rarely compare multiple drugs in the same study group, so rs-fMRI may provide a useful framework for comparing brain effects associated with different drugs, across multiple studies. Methods rs-fMRI data from five studies investigating brain effects of cannabis (N=16), ketamine (N=15), LSD (N=18), MDMA (N=23), and psilocybin (N=14) were analysed using a standardised pipeline. All data sets consisted of active (drug) scans, with accompanying placebo scans, in a within-subjects design. Functional connectivity analyses using the three major functional divisions of the striatum (associative, sensorimotor, and limbic) as seed-regions were conducted using FSL, for each set of study data. ICA-AROMA was used as a robust correction for subject head-motion, as well as other more standard pre-processing and analysis procedures, including high-pass filtering (100s), spatial smoothing (6mm) coregistration to a standard template (MNI152), and inclusion of noise regressors (mean white-matter and CSF signal). Subsequently PRoNTo (version 2.0; Schrouff et al., 2013, Neuroinformatics, 11(3), 319–337) was used to conduct Multi-Voxel Pattern Analyses (MVPA) of the resulting parameter estimates, comparing each set of drug data with its own placebo scans using leave one subject out cross-validation, and Gaussian Process Classification (GPC) models. The group-mean functional connectivity map from each set of analyses was used as a mask, and statistical significance was determined by permutation testing with 1000 iterations. Results Clear dissociations in the pattern of significant dissociations were evident across the six drugs investigated. Classification performance for MDMA was significant in all three analyses ($p<0.003$;

corrected threshold), but other drugs (LSD and THC+CBD; limbic only) were more selective in their effects. No significant effects were seen for the other drugs at the corrected significance threshold. Conclusions This novel approach to comparing pharmacological rs-fMRI data across multiple studies has revealed that different striatal networks may discriminate psilocybin, ketamine, LSD and cannabinoids from placebo. While comparisons across studies may never be as robust or strongly interpretable as those made within a single study, novel insights into the comparative neural effects of different drugs and their relation to the specific subjective effects of each may still result. This analysis project was supported by Imanova Ltd.

F02

SEROTONIN DEPLETION LESSENS THE BENEFIT OF MOTIVATIONALLY SALIENT FEEDBACK TO GUIDE BEHAVIOUR IN MALES

Kanen JW, Dept of Psychology, Cambridge Univ, Sir William Hardy Building Downing Street Cambridge, CB2 3EB jonathan.kanen@gmail.com

Apergis-Schoute AM(2), van der Flier FE(6), Yellowlees R(1), Arntz FE(1), Price A(7), Cardinal RN(4), Christmas DM(7), Sahakian BJ(3), Robbins TW(5)

(1) As presenting author; (2) Department of Psychiatry, Herchel Smith Buidling for Brain & Mind Sciences, Forvie Site, Robinson Way Cambridge CB2 0SZ, UK ; (3) Dept of Psychiatry, Herchel Smith Buidling for Brain & Mind Sciences, Forvie Site, Robinson Way Cambridge CB2 0SZ, UK ; (4) Dept of Psychiatry, Sir William Hardy Building, Downing Street, Cambridge; (5) Dept of Psychology, Downing Street Cambridge; (6) Heidelberglaan 1 Room H0.38 3584 CS UTRECHT, The Netherlands; (7) Liaison Psychiatry Service, Addenbrooke's Hospital, Cambridge Biomedical Campus, Cambridge CB2 0QQ

Flexibly adapting learned behaviours to maximize rewards and minimize punishments as circumstances change is critical for optimal functioning and wellbeing. This is modelled by instrumental reversal tasks whereby following the learning of a rule to guide behaviour, the contingencies are then reversed. Evidence from experimental animals suggests that serotonergic signalling is key for successful reversal learning (Clarke et al., 2004, Science, 304, 878-880) but findings in humans have been inconsistent (Murphy et al., 2002, Psychopharmacology, 163, 42-53; Evers et al., 2005, Neuropsychopharmacology, 30, 1138-1147), possibly because of task demands and salience of feedback. We hence employed a novel task with high cognitive demands, three reversals, and motivationally salient feedback, under a deterministic (100:0) reinforcement schedule. We used the dietary technique of acute tryptophan depletion (ATD), which temporarily lowers brain serotonin levels by depleting its precursor, tryptophan (Young et al., 1985, Psychopharmacology, 87, 173-177), in a double-blind randomized placebo-controlled between groups study. Healthy volunteers (n = 21, ATD; n = 21, placebo) learned an initial visual discrimination followed by three contingency reversals. This repeated in four counterbalanced conditions with neutral, rewarding, or punishing feedback. ATD did not impair reversal learning to criterion overall. An effect of serotonin depletion in male participants appeared at the second reversal of the most salient condition, when punishing and rewarding outcomes were reversed ($b=5.636$ $t(20)=2.876$, $p=0.009$). Whereas female participants irrespective of group (n=20), and males in the placebo group (n=11) benefited from the reinforcement history of rewards and punishments to update their subsequent behaviour, males under serotonin depletion (n=11) did not successfully make these adjustments. These findings represent a translational step across species, raise the possibility of gender differences, and advance our understanding of the role of serotonin in reward and punishment learning to guide adaptive behaviour. This work was supported by a Gates Cambridge Scholarship to J.W.K. and a Wellcome Trust Senior Investigator Grant 104631/Z/14/Z to T.W.R.

F03

USING BACLOFEN TO EXPLORE GABA-B RECEPTOR FUNCTION IN ABSTINENT ALCOHOL DEPENDENT AND HEALTHY VOLUNTEERS: INSIGHTS FROM PHARMACOKINETIC AND PHARMACODYNAMIC MEASURES

Durant CF, Centre for Neuropsychopharmacology, Imperial College London, Division of Brain Sciences, Department of Medicine, Hammersmith Hospital campus, London, W12 0NN c.durant@imperial.ac.uk

Turton S(1), Jones T(1), Nahar LK(2), Cordero RE(2), Paterson S(2), Nutt DJ(1), Wilson SJ(1), Lingford-Hughes AR(1)

(1) As presenting author; (2) Toxicology Unit, Imperial College London, London, W6 8RP

The role of GABA-B neurotransmission in alcohol use disorder (AUD) has received attention in recent years, with clinical trials indicating that baclofen (GABA-B receptor agonist) may reduce alcohol consumption, craving and promote abstinence. However, the reason why AUD patients require and tolerate much higher doses of baclofen (300mg vs 30mg), compared with other clinical uses, is poorly understood. As part of a series of studies probing GABA-B function, we have used PK/PD measures to provide insight into GABA-B sensitivity in this patient group. Male healthy volunteers (HV) (n=9) and abstinent alcoholics (ALC) (n=8) received single oral doses of baclofen & placebo (Vitamin C) in 3-way crossover design, with at least 1 week between each study day. HV received placebo/10mg /60mg baclofen in a randomised, double blind design, ALC received placebo/60mg/90mg baclofen in a single blind design. Measurements were taken at baseline & 0.5, 1, 2, 3, 4 and 6 hours following dosing. Objective/subjective measures included plasma baclofen, obtained using liquid chromatography mass-spectrometry, EEG and the Subjective High Assessment Scale (SHAS). Using change from baseline data, ANOVA analysis was used explore dose x time interactions within each group and between HV and ALC: t-tests were used to compare peak effects. For HV there was a main effect of baclofen for total (T) SHAS (TSHAS: $F(10,80)$ 2.311 $p=0.019$). This was driven by the 60mg dose, with a peak effect reported at 120mins compared with placebo (TSHAS 120min mean ± sem 144.4 ± 34.4 $p=0.03$). No significant changes were observed after 10mg (TSHAS 120min -7.4 ± 36.9, $p= 0.89$). Preliminary HV EEG data suggests an increase in theta activity after 60mg baclofen compared to baseline, which becomes evident at later time points. For ALC there was little subjective effect of baclofen (TSHAS n=6, ($F(10,50)$ 2.496 $p=0.13$), with 90mg, a trend for increased effect was noted at the final time points only. A direct comparison of ALC and HV at 60mg baclofen indicated a significant blunting in ALC scores compared with HV (TSHAS: interaction $F(5,75)$ 3.933 $p=0.01$, group pairwise comparison $p=0.014$). ALC & HV exhibited similar PK and AUC profiles at 60mg. Healthy volunteers exhibited a clear subjective response to 60mg baclofen, peaking at 2 hours. Abstinent alcoholics show a substantially blunted subjective response to 60 and 90mg baclofen, suggesting a lower GABA-B receptor sensitivity. These studies provide further insight into why higher doses of baclofen are requested by AUD patients for relapse prevention. This research was supported by MRC (G1002226) and the NIHR NHS Imperial CRF.

F04

NK1 ANTAGONISM ATTENUATES BLUNTED RESPONSE TO MONETARY REWARD ANTICIPATION IN ABSTINENT ALCOHOL DEPENDENCE

Paterson LM, Neuropsychopharmacology Unit, Imperial College London, Burlington Danes Building 160 Du Cane Road London, W12 0NN l.paterson@imperial.ac.uk

McGonigle J(1), Murphy A(3), Elliott R(3), Ersche KD(2), Flechais R(1), Orban C(1), Smith DG(2), Suckling J(2), Taylor EM(3), Deakin JFW(3), Robbins TW(2), Nutt DJ(1), Lingford-Hughes AR(1)

(1) As presenting author; (2) Behavioural and Clinical Neuroscience Institute, University of Cambridge, UK; (3) Neuroscience and Psychiatry Unit, Institute of Brain, Behaviour and Mental Health, University of Manchester, UK

Reward circuitry is known to be impaired in addiction, with evidence of a differential response to drug-related versus non-drug related rewarding stimuli in this population, relative to controls. Such dysregulation may contribute to relapse vulnerability. Novel treatments might therefore employ mechanisms to restore function by normalising the reward response to non-drug cues. NK1 receptors are predominantly located within the limbic system, particularly striatum, and may play a role in modulation

of reward processing. NK1 antagonists are implicated in the treatment of stress-related disorders and addiction. We investigated the effect of NK1 antagonism on reward anticipation using the monetary incentive delay (MID) task, a functional imaging probe of striatal function and non-drug reward sensitivity, in alcohol and polydrug dependence. Abstinent alcohol dependent (AD, n=19), polydrug dependent (PD, n=32) and matched control participants (n=33), recruited as part of the ICCAM study, received a selective NK1 antagonist (vofopitant or aprepitant, 10mg/80mg, oral) or placebo, 2 hours prior to fMRI scanning using the MID task. The task comprised win, neutral and loss trials in an event-related design. Reward anticipation (BOLD signal contrast between win and neutral anticipation) was investigated using whole brain voxelwise analyses (cluster corrected $Z > 2.3$, $p < 0.05$) and in region-of-interest (ROI) analyses in an a priori striatal region. Striatal activation in response to reward anticipation was blunted in both abstinent AD and PD groups relative to controls. NK1 antagonism attenuated this effect in the AD but not the PD group; whole-brain analyses revealed an increased BOLD response to win anticipation in striatum in the AD group and a significant drug by group interaction in this region, an effect which was also observed in the striatal ROI, where BOLD response to reward was restored in the AD but not the PD group. No effect of NK1 antagonism on reward anticipation was observed in controls. There were no significant drug or group effects on task performance. These data suggest that NK1 antagonism differentially modulates striatal response to reward anticipation in alcohol and polydrug dependence, with a potential utility emerging for NK1 antagonism to normalise non-drug reward sensitivity in abstinent alcohol dependence. This research was funded by the MRC, with additional financial support from GSK.

F05

REWARD DEFICIENCY IN ADDICTION: STRIATAL BLUNTING TO MONETARY REWARD AS A MARKER OF RECOVERY INSTABILITY

Paterson LM, Neuropsychopharmacology Unit, Imperial College London, Burlington Danes Building 160 Du Cane Road London, W12 0NN l.paterson@imperial.ac.uk

McGonigle J(1), Giribaldi B(1), Elliott R(3), Ersche KD(2), Flechais R(1), Orban C(1), Murphy A(3), Smith DG(2), Suckling J(2), Taylor EM(3), Deakin JFW(3), Robbins TW(2), Nutt DJ(1), Lingford-Hughes AR(1)

(1) As presenting author; (2) Behavioural and Clinical Neuroscience Institute, University of Cambridge, UK; (3) Neuroscience and Psychiatry Unit, Institute of Brain, Behaviour and Mental Health, University of Manchester, UK

Evidence suggests that impaired function in neural reward circuitry is a core feature of addiction. Thus, dysregulation of associated fronto-striatal networks may contribute to relapse vulnerability. Neuroimaging studies have shown that while alcohol or drug dependent individuals exhibit heightened striatal response to salient drug cues, they exhibit striatal blunting during reward anticipation to non-drug cues such as money, supporting the “reward deficiency” theory of addiction. It is not clear whether this represents a marker of predisposition to addiction, relapse vulnerability or some other trait. The ICCAM study sought to investigate mechanisms of addiction and relapse, to identify potential brain indices which could inform future treatments for relapse prevention. Using the monetary incentive delay (MID) task to measure brain responses to reward anticipation, we investigated whether the striatal BOLD response could provide a brain index of subsequent relapse in alcohol and polydrug dependence. Abstinent alcohol and/or polydrug dependent individuals (n=36), and matched control participants (n=33) underwent fMRI scanning (3-T) using the MID task at three research centres. Reward anticipation (BOLD signal contrast between win and neutral anticipation) was investigated using whole brain voxelwise analyses (cluster corrected $Z > 3.1$, $p < 0.05$) and a priori region-of-interest (ROI) analyses in striatum. Alcohol/polydrug dependent participants were followed up for 1 year after scanning, during which time n=23 remained abstinent and n=13 relapsed. In ROI analyses, striatal BOLD response to reward anticipation was significantly blunted in the relapse group relative to non-relapse and control groups (overall ANOVA $P=0.01$, with post-hoc Bonferroni correction, relapsers < abstainers $P=0.027$); there was no difference between controls and those who maintained abstinence for one year. Similarly, whole-brain analyses revealed an increased BOLD response to win anticipation in striatal regions in abstainers relative to relapsers. Relapsers also had significantly shorter abstinence duration prior to scanning than the abstinent group. Binary logistic regression revealed that both striatal BOLD signal change and abstinence duration were significant predictors of relapse within

1 year. The finding of a striatal blunting to monetary reward is in support of the “reward deficiency” hypothesis of addiction. The striking difference between the relapsers and abstinent/control groups suggests that blunted striatal response to reward anticipation may be a marker of recovery instability, contributing to relapse vulnerability. Novel treatments might therefore exploit this deficit by targeting mechanisms to restore function by normalising the reward response to non-drug cues. This research was funded by the MRC, with additional support from GSK.

F06

COMPARISON OF RESTING-STATE FMRI DATA FROM MULTIPLE DRUG STUDIES USING MULTI-VOXEL PATTERN ANALYSIS: CORTICAL NETWORKS

Verneuil T, Clinical Applications, Imanova Centre for Imaging Sciences, Burlington Danes Building Imperial College London Hammersmith Hospital Du Cane Road London, W12 0NN tessmv@hotmail.com

Gall A(6), Kowalczyk OS(2), Demetriou L(1), Roseman L(3), de Simoni S(5), Curran HV(4), Nutt DJ(3), Mehta MA(2), Carhart-Harris R(3), Wall MB(1)

(1) As presenting author; (2) Centre for Neuroimaging Sciences, Institute of Psychiatry (PO89), De Crespigny Park, London, SE5 8AF; (3) Centre for Neuropsychopharmacology, Division of Brain Sciences, Faculty of Medicine, Imperial College London, London W12, UK; (4) Clinical Psychopharmacology Unit, Research Department of Clinical, Educational and Health Psychology, University College London, Gower St, London, WC1E 6BT; (5) Computational, Cognitive and Clinical Neuroimaging Lab (C3NL),Division of Brain Sciences, Faculty of Medicine, Imperial College London, London W12, UK ; (6) Department of Psychology, Royal Holloway University of London, Egham, Surrey, TW20 0EX

Introduction Resting-state functional Magnetic Resonance Imaging (rs-fMRI) generally follows standardised procedures, and relies on universal underlying brain processes; this enables comparisons to be made across multiple studies (Biswal et al., 2010, PNAS, 107(10),4734-9). Pharmacological fMRI studies rarely compare multiple drugs in the same study group, so rs-fMRI provides a useful framework for comparing brain/drug effects across multiple studies. Methods rs-fMRI data from five studies investigating brain effects of cannabis (N=16), ketamine (N=15), LSD (N=18), MDMA (N=23), and psilocybin (N=14) were analysed using a standardised pipeline. All data sets consisted of active (drug) scans, with accompanying placebo scans, in a within-subjects design. Pre-processing used ICA-AROMA as a robust correction for head-motion, as well as more standard procedures (high-pass filtering, spatial smoothing, coregistration to a standard template). Twelve cortical resting state networks were independently defined using data from the Human Connectome Project: auditory, dorsal-attention, default-mode, left and right fronto-parietal, parietal, posterior-opercular, salience, sensorimotor, and three visual networks. These were used as the inputs to an ICA-based dual-regression analysis, which produced individualised versions of these networks for each subject/scan, across all five studies. Subsequently PRoNTo (version 2.0; Schrouff et al., 2013, Neuroinformatics, 11(3), 319–337) was used to conduct Multi-Voxel Pattern Analyses (MVPA) of these individualised network maps, comparing each set of drug data with its own placebo scans using leave one subject out cross-validation and Gaussian Process Classification (GPC) models. The original network definition map was used as a mask, and statistical significance was determined by permutation testing with 1000 iterations. Results Some drugs showed widespread effects on cortical resting-state networks; significant ($p<0.003$; corrected threshold) classification performance was seen in 11/12 networks for MDMA, and for 10/12 in LSD. Others showed more specific effects; only the sensorimotor network was significantly affected by ketamine in these analyses, and psilocybin only affected the left fronto-parietal network. The two strains of cannabis showed consistent effects on visual, salience, dorsal attention, and sensorimotor networks, and somewhat dissociable effects on other networks. Conclusions This novel approach to comparing pharmacological rs-fMRI data across multiple studies has revealed different cortical networks discriminate psilocybin, ketamine, LSD and cannabinoids from placebo. Such comparisons are not as robust or strongly interpretable as inferences made within a single study, however they may still potentially reveal differences in the neuropharmacological profile of each compound that could be useful in understanding the effects of psychotropic drugs. This analysis study was supported by Imanova Ltd.

F07

BLUNTED AMPHETAMINE-INDUCED OPIOID RELEASE IN INDIVIDUALS WITH GAMBLING DISORDER OR ALCOHOL DEPENDENCE COMPARED WITH HEALTHY VOLUNTEERS: A [11C]CARFENTANIL PET STUDY

Turton S, Neuropsychopharmacology Unit, Centre for Psychiatry, Imperial College London, Burlington Danes Building 160 Du Cane Road, w12 0nn s.turton@imperial.ac.uk

Mick I(3), Myers J(3), Colasanti A(5), Bowden-Jones H(6), Clark L(4), Rabiner EA(2), Gunn RN(1), Nutt DJ(3), Lingford-Hughes A(3),

(1) (1) Imanova Ltd, London, UK and (2) Centre for Restorative Neuroscience, Division of Brain Sciences, Imperial College London, UK; (2) (1)Imanova Ltd, London, UK and (2) Centre for Neuroimaging Sciences, King's College, London, UK; (3) As presenting author; (4) Centre for Gambling Research, Department of Psychology, University of British Columbia Vancouver, Vancouver, Canada; (5) Department of Neuroscience, Brighton and Sussex Medical School, University of Sussex; (6) National Problem Gambling Clinic, CNWL NHS Foundation Trust, Imperial College London, London, UK

Introduction There is evidence of endogenous opioid system dysregulation in gambling disorder (GD) and alcohol dependence (AD). Characterising this dysregulation is important as opioid receptor antagonists, such as naltrexone and nalmefene, are used to treat AD and GD. Higher mu-opioid receptor (MOR) availability has previously been shown to be positively associated with craving in AD and impulsivity in GD (Heinz et al., 2005, Arc Gen Psychiatry, 62:57-64, Mick et al., 2016, Neuropsychopharmacology, 41:1742–1750). We have shown that [11C]Carfentanil is a selective MOR agonist positron emission tomography (PET) radioligand sensitive to endogenous opioid/B-endorphin release following oral dexamphetamine (Colasanti et al., 2012 Biol Psychiatry, 72:371–377). We used this protocol to examine the hypothesis that both AD and GD are associated with blunted opioid/B-endorphin release and differences in baseline MOR availability compared with healthy volunteers (HV). Methods 13 male AD individuals (alcohol abstinence median 155 days, range 59-2920 days), 15 male GD individuals (gambling abstinence median 31 days, range 2-120 days) and 20 male HV were recruited. Both HV and GD consumed <21 UK units/168g of alcohol per week. Participants underwent two [11C]carfentanil PET scans, one before and one 3 hours following a 0.5 mg/kg oral dose of dexamphetamine. Dynamic PET data were acquired on a Siemens Biograph 6 for 90 minutes. [11C]Carfentanil regional binding potential (BPND) values (determined from a simplified reference tissue model, with the occipital cortex as the reference) were quantified using MIAKAT™ (www.miakat.org). An omnibus mixed-model ANOVA assessed BPND, ΔBPND, (= (Post-amphetamineBPND – Pre-amphetamineBPND)/Pre-amphetamineBPND), ROI (n=9, see Figure 1) and Group (AD, GD, HV). ROIs were chosen a priori as areas of importance in addiction, and with significant amphetamine-induced reductions of [11C]carfentanil BPND in previous studies. Results There was a significant main effect of Group on [11C]carfentanil ΔBPND ($p=0.04$). Post-hoc tests show a significant difference between HV and AD ($p=0.001$), HV and GD ($p=0.022$) but not between GD and AD ($p=0.193$). There is a non-significant trend of smaller ΔBPND values in AD. There is no significant effect of Group on baseline [11C]carfentanil BPND ($p=0.238$). Conclusions Both AD and GD demonstrated blunted amphetamine-induced opioid/B-endorphin release compared with HV, but no differences in baseline MOR availability. Our finding of similarly blunted opioid/B-endorphin release in AD and GD suggests this may be fundamental to addiction rather than as a result of chronic alcohol exposure. This research was supported by MRC (G1002226) and the NIHR NHS Imperial CRF.

F08

ASSOCIATION OF METHAMPHETAMINE DEPENDENCE WITH A GENETIC VARIANT OF GRIA3 GENE AND ITS INTERACTION WITH A FUNCTIONAL BDNF POLYMORPHISM

Iamjan SA, Department of Anatomy and Centre of Excellence in Medical Biotechnology, Faculty of Medical Science, Naresuan University, Muang Phitsanulok, Phitsanulok, Thailand, 65000 sriaruni55@hotmail.com

Thanoi S(1), Watiktinkorn P(2), Reynolds GP(1), Nudmamud-Thanoi S(1),

(1) Biomolecular Sciences Research Centre, Sheffield Hallam University, Sheffield, S1 1WB, UK; (2) Synphaet Hospital, Bangkok, Thailand

Introduction: Methamphetamine (METH) is an addictive psychostimulant drug; repeated doses of METH can commonly induce schizophrenia-like psychotic symptoms. Dysregulation of the glutamatergic system may be involved in METH dependence and its consequences, and the alpha (α)–amino-3 hydroxy-5 methyl-4 isoxazole propionic acid (AMPA) glutamate receptor has been implicated in these neurobiological mechanisms. AMPA receptors play critical roles in neuronal synaptic plasticity of learning, memory and addiction and genetic variants of genes encoding AMPA receptor subunits, GRIAs, have been associated with psychosis. The aim of this study was to examine the association of genetic variants of GRIA genes with METH dependence and METH-dependent psychosis. Method: Genotyping of GRIA1 rs1428920, GRIA2 rs3813296, GRIA3 rs3761554, rs502434 and rs989638 was performed in 102 male Thai controls and 100 METH-dependent subjects (53 with METH-dependent psychosis). Inter-group statistical differences in allele and genotype frequencies were analyzed by Chi-square test. P values less than 0.05 were considered statistically significant and Bonferroni correction was applied to results involving the three polymorphisms of GRIA3. Results: Chi-square analysis showed nominal associations of GRIA3 rs502434 with METH dependence (p=0.049) and METH-dependent psychosis (p=0.023) when compared to controls. The G allele had a higher frequency in both METH dependence and METH-dependent psychosis, although the results did not withstand Bonferroni correction for multiple testing (p>0.05). However, combination of results at this site and the previously-demonstrated association with the functional BDNF rs6265 (Iamjan et al., 2015, Pharmacogenomics, 16, 1541-5) showed a highly significant effect on METH dependence, in which carriage of one or both of the respective GRIA3 G or BDNF GG genotypes greatly increases risk (p<0.001; odds ratio=2.77). For other polymorphisms investigated, there were no significant associations with METH dependence or its psychosis. Conclusion: Combination of the GRIA3 polymorphism rs502434 and BDNF rs6265 is strongly associated with METH dependence in this Thai sample. This study was financially supported by grants from the Royal Golden Jubilee Ph.D. program and Naresuan University Research Fund.

F09

MOTIVATIONAL PROCESSING OF CIGARETTE AND MUSIC REWARD IN DEPENDENT AND OCCASIONAL SMOKERS: AN FMRI AND BEHAVIOURAL STUDY

Lawn W, Clinical Psychopharmacology Unit, University College London, 1-19 Torrington Place, London, WC1E 7HB will.lawn@ucl.ac.uk

Freeman TP(1), Bisby JA(2), Dodds CM(3), Curran HV(1), Morgan CJA(3)

(1) As presenting author; (2) Institute of Cognitive Neuroscience, University College London, UK; (3) Psychopharmacology and Addiction Research Centre, University of Exeter, UK

Introduction: Nicotine dependence is thought to be associated with a hypersensitivity to cigarette reward and a hyposensitivity to non-drug reward. Both heighted sensitivity to drug rewards and reduced sensitivity to non-drug rewards may contribute to the maintenance of addiction. However, little research has evaluated drug and non-drug rewards within the same paradigm (see notable exceptions1,2). Furthermore, money is often used as the non-drug reward, which can be exchanged for cigarettes. Therefore, it is potentially advantageous to use consummatory non-drug rewards. Methods: Twenty-two dependent smokers and 20 occasional smokers (following ad libitum smoking) completed an adapted incentive delay task (AIDT), in which cigarettes and music reward could be won. In this task, during functional magnetic resonance imaging (fMRI) participants are shown a cue (for cigarette or music) and then must respond to a target in a set amount of time. If they respond quickly enough, points for real rewards are accrued. The neural correlates of anticipation and feedback are considered neural metrics of motivational processing. An ROI analysis and whole brain analysis were carried out. Moreover, behavioural motivation was assessed using reaction time to the target. Results: Groups were well matched for age, gender and verbal IQ. Dependent smokers, compared with occasional smokers, were faster to respond on cigarette trials (t40=2.27, p=0.027). There were no differences on music and no reward trials. Both the dependent smokers (t19=2.583, p=0.043) and the occasional smokers (t21=3.46, p=0.003) were faster to respond on music compared with no reward trials. The dependent smokers (t21=3.75, p=0.001), but not occasional smokers (t19=1.25, p=0.664), were faster to respond on cigarette compared with no reward trials. Anticipation of cigarette reward, in both groups, led to significant activation in

the left ventral striatum, bilateral thalamus and left medial frontal gyrus ROIs. There were no significant differences between the groups in BOLD response during cigarette anticipation. Positive feedback about cigarette reward, in both groups, led to significant activation in the right caudate, left amygdala and left parahippocampal region ROIs. Importantly, dependent smokers showed greater activation in the right caudate than occasional smokers during positive feedback about cigarette reward (p=0.045). There were no group differences in BOLD response to music anticipation or feedback. Conclusions: On a behavioural level, nicotine-satiated dependent smokers, compared with occasional smokers, have a greater motivation for cigarette but not music reward. Furthermore, dependent smokers exhibited a stronger BOLD response than occasional smokers to positive cigarette reward feedback in the right caudate compared. Thus, we demonstrated both behavioural and neural hypersensitivity to drug reward in nicotine dependence. However, we did not find evidence for non-drug hyposensitivity between the groups. The role non-drug reward processing plays in nicotine dependence must be further examined. This research was funded by a BBSRC studentship.

F10

THE EFFECTS OF LONG-TERM MDMA USE ON RESPONSES TO SOCIAL EXCLUSION

Carlyle M, Psychology, The University of Exeter, Washington Singer, Psychology Building, Perry Road, Exeter, EX4 4QG M.Carlyle@exeter.ac.uk

Stevens T(1), Morgan CJA(1)

(1) As presenting author

Introduction 3,4-methylenedioxy-N-methylamphetamine (MDMA) has recently been highlighted for its positive effects on fundamental social processes, such as empathy and compassion (Hysek et al., 2014; Kamboj et al., 2015). Acutely, MDMA has also been shown to attenuate the impact of negative social events, such as reducing the drop in mood and self-esteem following social exclusion (Frye et al., 2014). These effects have highlighted the potential therapeutic benefit of MDMA, however there is little research looking at how chronic MDMA use may impact these processes. Method 75 Participants were divided into three categories based on their drug use history, and met the criteria for either: chronic MDMA users (n= 24); other illicit drug users (n=23); or alcohol users only (n=28). All participants then played a computerised game that covertly simulated both social inclusion and exclusion ('the Cyberball Paradigm'; Williams et al., 2012), and assessments of mood, self-esteem, and inclusion estimates were taken following each game. Results As expected, all groups shown a significant reduction in both positive mood ($p<.001$) and self-esteem ($p<.001$), and a significant increase in negative mood ($p<.001$) following a period of social exclusion. However, these did not significantly differ between groups ($p=.459$, $p=.115$, $p=.327$, respectively). No indices of MDMA use (last used, recent use, amount used in typical session, length of use) correlated with mood, self-esteem, or perceived inclusion status after being included/excluded. Conclusions Chronic MDMA users in this sample exhibited normal psychosocial functioning. This stands in contrast to what is observed when given acutely (Frye et al., 2014). Equally, chronic MDMA use was not found to cause any adverse consequences to the perception and impact of these negative social events, which contests previous concerns that long-term MDMA use may cause heightened social distress (Parrott, 2007). These findings are valuable from a therapeutic perspective, since they help elucidate the long-term effects of MDMA on fundamental interpersonal processes. This project was funded by the University of Exeter.

F11

USING THE NMDA RECEPTOR ANTAGONIST NITROUS OXIDE TO PROBE THE PARAMETERS DETERMINING CUE-ALCOHOL MEMORY DESTABILISATION IN HEAVY DRINKERS

Walsh KH, UCL, 1-19 TORRINGTON PLACE, LONDON,, WC1E 7HB katie.walsh.14@ucl.ac.uk

Das RK(1), Hannaford JR(1), Kamboj SK(1)

(1) As presenting author

Introduction Maladaptive motivation memories (MMM) are formed when cues in the environment become classically and instrumentally associated with the pleasant effects of alcohol consumption. While

it was previously assumed that once formed these memories could not be altered, research into memory reconsolidation suggests that these memories can be reactivated and subsequently modified. The current study used N2O, an NMDAR antagonist, to explore the parameters determining MMM destabilisation in heavy drinkers. It was predicted that MMM would be successfully destabilised following memory reactivation and the generation of a prediction error, and that reconsolidation of alcohol memories would be blocked by inhalation of N2O. Methods The current study utilised three groups, with one group experiencing reactivation and prediction error (N=21), another only undergoing reactivation (N=19) and the final experiencing only prediction error (N=20). All groups received N2O. Measures of alcohol consumption and physiological measures of attentional bias were recorded. Results Participants who experienced MMM reactivation and prediction error did not score significantly lower than the other groups on measures of alcohol consumption, liking, or craving. No difference between groups on attentional bias towards alcohol cues was also recorded. There was however a significant difference over time on the AUDIT, with scores significantly declining only in the group which experienced both prediction error and MMM reactivation (p=0.011). Conclusion These null findings conflict with previously reported results and suggest that N2O may not to be sufficiently potent to successfully block memory reconsolidation. This research was funded by an MRC project grant to SKK and RKD.

F12

QUANTIFYING VIOLENT CRIME ASSOCIATED WITH ALCOHOL USE AMONG A LARGE COHORT OF SANCTIONED OFFENDERS IN ENGLAND AND WALES

McGrath E, DNEP, University of Manchester, G.803 Stopford Building, Oxford Road, Manchester, M13 9PT ellylouisemcgrath@gmail.com

Lightowlers C(3), Pierce M(2), Millar T(1)

(1) 4th Floor, Block C, Ellen Wilkinson Building, The University of Manchester, Oxford Road, Manchester, M13 9PL ; (2) Jean McFarlane Building-Centre for Biostatistics, The University of Manchester, Oxford Road, Manchester, M13 9PL ; (3) School of Law The Liberty Building University of Leeds Leeds LS2 9JT

Introduction/Aim To assess the relationship between alcohol use and prior violent offending. Methods 40,005 persons (107,573 men) identified from a saliva test for opiate and cocaine metabolites following arrest in England and Wales, 1 April 2005–31 March 2009, were case-linked with 2-year recorded offending history. The prior violent offending rate, accounting for estimated incarceration periods, was calculated by: drug-test outcome and gender. Rate ratio (RR) compared offenders with alcohol only problems, drug only problems, alcohol and drug problems and no problems. Adjusted rate ratio (aRR) controlled for age at drug test. Results The rate of 2-year prior (sanctioned) violent offending, as assessed using a negative binomial regression model, was greater among those classified as having problems with alcohol use (with or without concurrent drug problems) than for gender-matched cases with drug use only problems, in comparison to those with no problems. The adjusted rate ratios showed that men using only alcohol committed 1.75 times more violent offences than those with no alcohol or substance use ($p<0.001$), men using both drugs and alcohol committed 1.62 times more violent offences ($p<0.001$) than those with no alcohol or substance use and men using only drugs committed 0.95 times more violent offences ($p=0.177$) than those with no alcohol or substance use. Women using only alcohol committed 3.05 times more violent offences than those with no alcohol or substance use ($p<0.001$), women using both drugs and alcohol committed 2.39 times more violent offences ($p<0.001$) than those with no alcohol or substance use and women using only drugs committed 1.11 times more violent offences ($p=0.316$) than those with no alcohol or substance use. In women the difference was particularly pronounced, with women who were classified as having problems with alcohol use only having prior violent offending rates at three times higher than their gender-matched counterparts who were classified as having no problems. Conclusions Among drug-tested offenders, alcohol use is associated with elevated prior violent offending and the association is stronger for women than men. No sponsorship was received for this study.

F13

HOSPITAL ATTENDANCE AND ADMISSION AS AN OPPORTUNITY TO ENGAGE PATIENTS WITH ALCOHOL USE DISORDERS

Chambers SE, Clinical and Experimental Sci, Fac of Medicine, Univ of Southampton, Academic Centre, College Keep, 4-12 Terminus Terrace, Southampton, SO14 3DT sec1n14@soton.ac.uk

Baldwin DS(1), Lo R(2), Williams S(2), Sinclair JMA(1)

(1) Clinical and Experimental Sci, Univ Dept of Psychiatry, Southampton, SO14 3DT; (2) Fac of Medicine, Univ of Southampton, Southampton, SO14 3DT

INTRODUCTION Excessive alcohol consumption is associated with multiple health problems, and frequently results in use of secondary care services. The emergency department presents an environment to engage patients in discussion about their alcohol use. It is unclear whether patients who present to the emergency department but are not admitted, have a different behavioural profile and readiness to change their drinking, when compared to patients admitted for elective or emergency inpatient care. METHODS An observational cohort study of 124 patients with alcohol use disorders (AUD) presenting to Southampton General Hospital (September 2016 – March 2017) were recruited from one of two teams: a Vulnerable Adult Support Team (n=39, mean age 45.8 years) based in the emergency department (ED outpatient group, EDOP), and a pan-hospital nurse-led Alcohol Care Team (n=85, mean age 53.3 years) who assess and support patients during an admission (inpatient group, IP). Patients were assessed on measures including: alcohol use and psychological dependence, readiness to change, psychological distress and current treatment engagement (defined as attendance at a community substance misuse service or mutual-aid support group within the past month). They were also asked whether this occasion marked the first time a healthcare professional had assessed their alcohol use in a hospital setting, and then to evaluate the assessment on a 5-point Likert scale (1 = very negative, 3 = neutral, 5 = very positive). Differences between groups were evaluated using independent sample Mann Whitney U tests and Chi-square analyses. RESULTS EDOP patients had significantly higher Alcohol Use Disorder Identification Test scores (p=.035), psychological dependence on alcohol (p=.044), and psychological distress (p=.005). This group also reported significantly lower readiness to change their drinking (p=.001). Only 17.7% of all patients (n=124) reported current engagement in treatment, and for 41.9%, this was the first assessment of their alcohol use; furthermore, 77.5% of the cohort rated the assessment as ‘positive’ or ‘very positive’ (a further 17.7% rated it as ‘neutral’). CONCLUSIONS These findings suggest that hospital attendance and admission presents an opportunity to engage patients in discussions about their alcohol use, often for the first time. Patients attending an emergency department represent a group who would benefit from intervention to increase motivation to change their drinking, alongside support to address their high levels of psychological distress. The relative efficacy of various strategies to engage patients is yet to be compared at different points of the clinical care pathway. FUNDING This project was funded as part of SEC’s PhD studentship (Wessex Academic Health Science Network in partnership with H. Lundbeck A/S).

F14

ULTRA-BRIEF MINDFULNESS TRAINING REDUCES ALCOHOL CONSUMPTION IN AT-RISK DRINKERS: A RANDOMISED DOUBLE-BLIND ACTIVE-CONTROLLED EXPERIMENT

Thomas ET, Clinical, Educational, and Health Psychology, University College London, 1-19 Torrington Place UCL London, WC1E 7HB em.morgan.thomas@gmail.com

Kamboj SK(1), Irez D(1), Serfaty S(1), Das RK(1), Freeman TP(1)

(1) As presenting author

Introduction Like other complex psychosocial interventions, mindfulness-based treatments comprise various modality-specific active components, as well as non-specific therapeutic ingredients that collectively contribute to efficacy. Consequently, the isolated effects of mindfulness strategies per se remain unclear. Methods Using a randomised double-blind design, we compared the isolated effects of 11 min of mindfulness instruction against a closely-matched active control (relaxation) on subjective, physiological and behavioural indices of maladaptive alcohol responding in drinkers at-risk of alcohol use disorder (n=68). Statistical analyses were completed using independent samples t-tests and mixed

ANOVAs. Results Whereas the relaxation group showed larger acute reductions in craving (d=0.574, p<0.001) and upregulation of parasympathetic activity (p < 0.001), only the mindfulness group showed significantly reduced alcohol consumption at follow-up (-9.31 units; p<0.001, d=0.597). Conclusions Even ultra-brief mindfulness instructions can have pronounced effects on self-regulation of drinking behaviour, independently of effects on craving. Given their unique mechanism of action, additive or synergistic effects might be expected if mindfulness strategies are combined with existing brief interventions for alcohol use disorders. Funded by University College London, no external sponsorship was received for the study.

F15

DEVELOPMENT OF A BRIEF COMPASSION TRAINING TO ASSIST OPIATE ADDICTION RECOVERY.

Rockliff H, Psychopharmacology and Addictions Research Centre, University of Exeter, St Luke's Campus Heavitree Road Exeter, EX1 2LU h.rockliff@exeter.ac.uk

Carlyle M(2), Karl A(1), Edwards R(4), Morgan C(3)

(1) Mood Disorders Centre, Washington Singer Laboratories, University of Exeter, Perry Road, Prince of Wales Road Exeter EX4 4QG; (2) Psychopharmacology and Addictions Research Centre, University of Exeter, St Luke's Campus Heavitree Road,EX1 2LU; (3) Psychopharmacology and Addictions Research Centre, Washington Singer Laboratories, College of Life and Environmental Sciences, University of Exeter Perry Rd, Exeter, EX4 4QG; (4) Recovery and Integration Service (RISE) Uplands, 81, Heavitree Road. EX1 2LX

Introduction Self-compassion is an important predictor of wellbeing and resilience (MacBeth et al., 2012 Clinical Psychology Review, 32, 545-552). Research also suggests interventions to develop self-compassion are beneficial for a range of different psychological problems. Some evidence from alcohol drinkers (Brooks et al., 2012 Mindfulness, 3, 308-317) and tobacco smokers (Kelly, et al., 2010 Journal of Social and Clinical Psychology, 29, 727-755) also suggests such interventions may be helpful for addiction recovery. This project therefore aimed to develop and pilot a brief self-compassion training intervention to assist recovery from opiate addiction. Methods The intervention content was developed in collaboration with staff and clients from addiction services in Devon, in order to identify feasible content for a 5-hour course held over 3 weeks.. Participants (n=21) currently receiving opiate substitution prescriptions were recruited via their keyworker and then allocated to either the self-compassion training course or an active control group consisting of basic relaxation exercises. Measures of drug craving, depression, anxiety, self-criticism and self-compassion were recorded before and immediately following intervention. All participants were also interviewed to obtain qualitative data on intervention acceptability and to understand barriers and facilitators to participation for larger trials or service run group interventions. Results Repeated measures ANOVA revealed a decrease in anxiety (p=.012) and depression (p=.037) for both groups, but no significant differences between the compassion and relaxation groups. Thematic analysis of the qualitative data indicated that the acceptability of both interventions was good. Conclusions It is possible to engage clients recovering form opiate addiction with a brief self-compassion training intervention. Preliminary analysis of the data indicates that the intervention is beneficial for improving mood, but only as effective as an active control intervention. As a result of this study, addiction support services in Devon are using both interventions for future delivery. Piloting this intervention has also generated useful feasibility data for informing future larger-scale RCTs or service rollout to this client group. Funding: Economic and Social Research Council, Project Co-Creation Grant.

F16

ANATOMY OF A JOINT: COMPARING SELF-REPORTED AND ACTUAL DOSE OF CANNABIS AND TOBACCO IN A JOINT, AND HOW THESE ARE INFLUENCED BY CONTROLLED ACUTE ADMINISTRATION

Hindocha C, Clinical Psychopharmacology Unit, University College London, 1-19 Torrington Place, London, Wc1E 7HB c.hindocha@ucl.ac.uk

Freeman TP(1), Curran HV(1)

(1) Clinical Psychopharmacology Unit, University College London, WC1E 7HB

Introduction: Cannabis use metrics are a proxy for exposure to THC, however, major gaps exist in the measurement of cannabis exposure. In Europe, but also worldwide, users often mix cannabis with tobacco, which may modify the cannabis dose, subjective experience and cognitive effects and is often unaccounted for. Using a novel 'Roll a Joint' paradigm, this study aims to (1) compare estimated and actual dose of cannabis and tobacco per joint at baseline, (2) to examine the acute effects of cannabis and/or tobacco on estimated and actual dose. Method: A randomised, double-blind, placebo-controlled, 2(cannabis, placebo) x 2(tobacco, placebo) crossover of medically and psychiatrically healthy recreational cannabis and tobacco (i.e. joint) smokers (N=24) was conducted. Participants attended 4 sessions, separated by one week. At baseline, participants were asked to measure out the amount of cannabis (using a placebo substitute; which looks and smells like cannabis but with cannabinoids removed), and tobacco they would put in an average joint for themselves (dose per joint).On each of 4 drug administration sessions, participants were again asked to do this for a joint they would want to smoke 'right now'. Self-reported and actual amount were recorded (g). Results: Participants were minimally dependent on cannabis or tobacco. At baseline, the estimated amount of cannabis per joint (0.28 ± 0.23g) was double the actual amount (0.14 ± 0.12g) ($p=0.003$ $d=0.723$). No difference emerged between estimated (M:0.43, SD:0.25) and actual (M:0.35, SD:0.15) ($p=0.125$) dose of tobacco per joint. Compared to placebo, after smoking active cannabis, participants reduced the actual dose of both cannabis ($p=0.035$) and tobacco ($p<0.001$) per joint. Participants accurately estimated the reduced tobacco consumption ($p=0.014$), but not the reduced cannabis consumption ($p=0.68$). Conclusions: Recreational cannabis users, when sober, showed a 2-fold overestimation between the estimated and actual dose of cannabis in a joint but accurately estimated dose of tobacco in the same joint. This was replicated across each drug condition suggesting this overestimation bias was not sensitive to acute drug administration. However, after smoking active cannabis, the dose of both cannabis and tobacco in the joint reduced, suggesting this paradigm is sensitive to satiety effects. Finding accurate and standardised cannabis use metrics is essential to monitor levels of cannabis and tobacco consumption. In Europe, the particular issue of smoking cannabis and tobacco is worrying and mostly disregarded. This research was funded by an MRC studentship to CH.

F17

CANNABIS POTENCY AND CANNABIS USE DISORDERS: A CROSS-SECTIONAL STUDY INDEXING CANNABINOIDS AND THEIR METABOLITES IN CANNABIS, URINE AND HAIR

Freeman TP, National Addiction Centre, King's College London, National Addiction Centre Institute of Psychiatry, Psychology & Neuroscience King's College London 4 Windsor Walk, London, SE5 8BB, UK tom.freeman@kcl.ac.uk

Morgan CJ(2), Hindocha C(1), Shaban N(1), Das RK(1), Curran HV(1)

(1) Clinical Psychopharmacology Unit, University College London, Gower St, London, WC1E 6BT; (2) Department of Psychology, University of Exeter, Washington Singer Building, Perry Road, Exeter, EX4 4QG

Introduction: High potency cannabis containing elevated levels of THC (Δ9-tetrahydrocannabinol) and no cannabidiol (CBD) increasingly dominates street-markets globally (Curran HV et al., 2016, Nature Reviews Neuroscience, 17, 293-306). Preliminary findings from an online survey suggest that use of high potency cannabis is associated with an increased severity of dependence (Freeman TP & Winstock AR 2015, Psychological Medicine, 45, 3181-3189). However, that study lacked a clinical measure of cannabis use disorders, was unable to verify self-reported cannabis potency, and did not adjust for additional measures of cannabis and tobacco use. Methods: 410 cannabis users were tested once when intoxicated with their own cannabis and once when drug-free. Their cross-sectional preference for different cannabis strains was assessed alongside DSM-IV-TR cannabis abuse/dependency and the Severity of Dependence Scale (SDS). Cannabis potency/exposure was measured objectively by analysing CBD, THC and its metabolites in each participants' own cannabis, urine and hair. Results: After adjusting for demographics and a comprehensive set of cannabis and tobacco use measures, preference for high potency cannabis predicted a 2.1-fold increased incidence of cannabis dependence (OR=2.056, 95% CI=1.019 to 4.148, $p=0.044$) and a 2.4 fold increase in cannabis abuse (OR=2.413 95% CI=1.136 to 5.129, $p=0.022$). Frequency of use predicted all abuse/dependence measures, and urinary THC metabolites predicted SDS scores (B=0.003, 95%

CI=0.001 to 0.004, p<0.001). High potency preference was associated with higher THC concentrations in the cannabis users actually smoked (p=0.008), as well as THC metabolites in urine (p<0.001) and hair (THC: p=0.024; THC-OH: p<0.001). Conclusions: Preference for high potency cannabis is associated with a two-fold increased risk of cannabis use disorders, and with elevated cannabinoids/cannabinoid metabolites in cannabis, urine and hair. Severity of cannabis dependence was predicted by increasing levels of THC metabolites in urine. These findings do not provide evidence for causality. However, they highlight the potential importance of cannabis potency for the public health impact of cannabis use, and for policy decisions to minimise harm. Funding: UK Medical Research Council (G0800268).

F18

MAKING HEALTHIER FOOD CHOICES: EXAMINING THE CONTRIBUTION OF GOAL-DIRECTED AND HABITUAL DECISION SYSTEMS TO FOOD SELECTION

Ziauddeen H, Psychiatry, University of Cambridge, Douglas House 18b Trumpington Road Cambridge, CB2 8AH hz238@cam.ac.uk

Medic N(1), Forwood SE(3), Ahern AL(5), Davies KM(4), Jebb SA(6), Marteau TM(2), Fletcher PC(1)

(1) As presenting author; (2) Behavioural and Health Research Unit, University of Cambridge; (3) Dept. of Psychology, Anglia Rusking University; (4) Dept. of Psychology, University of Cambridge; (5) MRC Epidemiology Unit, University of Cambridge; (6) Nuffield Dept. of Primary Care Health Sciences, University of Oxford

Introduction: Despite being informed and motivated, many people struggle to consistently make healthy food choices Using knowledge and motivation to make healthy choices requires the brain's deliberative, goal-directed decision system. However most food decisions are likely made by the more automatic habitual decision system, using past experience to make rapid, efficient but inflexible, context- and stimulus-driven choices. Using a novel grip force task that taps into these habitual preferences and a widely used measure of goal directed food decision-making, we examined these systems' contribution to the healthiness of real world food choices. Methods: 63 age-, sex- and SES-matched healthy participants (20 lean, 43 overweight-obese) underwent MRI scanning while performing: (1) a goal-directed task in which they made a series of choices between a reference neutral food and several other foods, (all previously rated for healthiness and tastiness) (2) a habit-directed food preference task, in which they squeezed a grip force bulb to indicate how much they wanted each food item on the screen if they could have it at that moment. We estimated the contribution of healthiness to goal-directed choices (βHealth) and habitual health preference (effort exerted for healthy compared to unhealthy foods) from the behavioural and neuroimaging data for each task; and examined the degree to which these measures predicted the healthiness of participants' food choices at a buffet lunch at the end of the study. Separate linear models were used for the behavioural and neuroimaging data. Results: The value computation signal in the goal-directed task was found in the ventromedial prefrontal cortex and the health preference signal in the habit-directed grip force task was found in the medial prefrontal cortex (both at FWE p<0.05). The neural βHealth and health preference parameter estimates were extracted from the respective clusters. Health preference (behavioural, r=0.58, p<0.0001; neural, r=0.43,p<0.01) and βHealth (behavioural, r=0.44,p<0.01; neural r=0.37, p<0.05) correlated strongly with the percentage of healthy buffet choices. However the habit-driven health preference (behavioural 33%, p<0.0001; neural 23%, p<0.0001) explained a greater percentage of the variance in healthy choices than the goal-directed βHealth (behavioural 1.4%, n.s.; neural 9.3%, p<0.01). Overweight-obese status was an independent predictor of fewer healthy choices (behavioural 16.6%, p<0.01; neural 7.2%, p<0.01). Conclusions: These findings suggest in the presence of real food, habitual preferences have a greater influence on choices than goal-directed ones, with the healthiness of these preferences determining the healthiness of food choices. This has important implications for health policy, which is more heavily focussed on goal-directed than habit-directed decision-making. Funding: This study was funded by the Wellcome Trust through a Senior Fellowship to PC Fletcher and a PhD fellowship to N Medic.

F19

EFFECTS OF STIMULANTS ON THE HUMAN DOPAMINE SYSTEM: A META-ANALYSIS AND IMPLICATIONS FOR DRUG DEVELOPMENT AND PRECLINICAL MODELS

Ashok AH, Psychosis studies, Institute of Psychiatry, Psychology and Neurosciences, Institute of Psychiatry, Psychology & Neuroscience King's College London 16 De Crespigny Park London +44 (0) 20 7848 0002, SE5 8AF abhishekh.ashok@kcl.ac.uk

Mizuno Y(1), Volkow ND(2), Howes OD(1)

(1) As presenting author; (2) National Institute on Alcohol Abuse and Alcoholism and National Institute on Drug Abuse, Bethesda, USA

Background: Stimulant abuse or dependence is common, affecting between 0.3 to 1.1% of the population, and costs over $85 billion per year globally. There are currently no licensed treatments. Several lines of evidence implicate the dopamine system. Thus understanding the nature of dopamine dysfunction seen in stimulant users has the potential to aid the development of new therapeutics. We reviewed the in-vivo imaging evidence for dopaminergic alterations in stimulant (cocaine or amphetamine/methamphetamine) drug abuse or dependence. Method: The PubMed, EMBASE and PsycINFO databases were searched for studies from inception date to May 14, 2016. A total of 31 studies were identified that compared dopaminergic measures between 519 stimulant users and 512 controls using positron emission tomography or single-photon emission computed tomography to measure striatal dopamine synthesis or release, or dopamine transporter or receptor availability. Demographic, clinical and imaging measures were extracted from each study and meta-analyses and sensitivity analyses were conducted for stimulants combined and cocaine and amphetamines separately where there were sufficient studies. We determined the difference in dopamine release, transporter and receptor availability in cocaine, amphetamine and methamphetamine users and healthy controls. Results: There was a significant decrease in striatal dopamine release (stimulants combined: Hedge's g= -0.84; cocaine: -0.87, both $p<0.001$), dopamine transporter availability (stimulants combined: Hedge's g= -0.91, $p<0.01$; amphetamine and methamphetamine: Hedge's g: -1.47, $p<0.001$) and D2/3 availability (stimulants combined: Hedge's g= -0.76; cocaine: -0.73; amphetamine and methamphetamine: -0.81, all $p<0.001$). We did not find consistent alterations in vesicular monoamine transporter, dopamine synthesis or D1 receptor studies. Conclusion: Our data suggest that both pre and post-synaptic aspects of the dopamine system are down-regulated in stimulant users. We discuss the commonality and difference between these findings and the discrepancies with the preclinical literature as well as their implications for future drug development. Funding: This study was funded by the Medical Research Council and King's College London. Funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

F20

GENDER DIFFERENCES IN KAPPA OPIOID RECEPTOR ACTIVATED BRAIN NETWORKS IMPLICATED IN THE RESPONSE TO STRESS AND DRUGS OF ABUSE

Ma Q, Dept of Pharmacy and Pharmacology, Univ of Bath, Claverton Down BATH, BA2 7AY qm207@bath.ac.uk

Wonnacott SW(1), Bailey SJ(2), Bailey CP(2)

(1) Department of Biology and Biochemistry, Claverton Down, BATH BA2 7AY; (2) Dept of Pharmacy and Pharmacology, Claverton Down, BATH BA2 7AY

Stress is a risk factor for the development of drug addiction and relapse back to drug taking. Kappa opioid receptors (KOPrs) are involved in both stress responses and addiction-related behaviour (Bruchas et al., 2010, Brain Research, 1314:44-55). It has been shown that the role of KOPrs in motivated behaviour is sex dependent (Russell et al., 2014, Bio Psychiatry 76:213-222). This study aimed to investigate the influence of gender on the activation of KOPrs in brain regions that are activated by stress. Expression of the immediate early gene c-Fos is a neuronal marker of recent neural activity. Using C57BL/6 c-Fos-GFP transgenic mice, in which expression of green fluorescent protein (GFP) is driven by the activation of c-Fos (Barth et al., 2004, Journal of Neuroscience 24:6466-75), we have investigated the response to KOPr activation using the agonist U50,488 in multiple brain regions in both genders. Adult- (8-11wks) male

and female C57BL/6 cFos-GFP transgenic mice were injected (i.p 10ml/kg) with saline or KOPr antagonist norBNI (10mg/kg). After 24 hours, these mice were treated with either saline or KOPr agonist U50,488 (20mg/kg). Two hours later, mice underwent transcardial perfusion fixation under terminal anaesthesia and brains were removed. Brain sections (40μm) were immunolabelled to assess cFos and cFos-driven GFP expression and quantified by fluorescence microscopy. U50,488 significantly increased the expression of both cFos and GFP in nucleus accumbens (NAcc) ($P<0.01$) and prelimbic area of the prefrontal cortex (PFC) ($P<0.05$) in male mice, compared to saline treated controls. These brain regions were not activated in female mice. In the CA1 region of the dorsal hippocampus (CA1), cFos, but not GFP, expression was significantly increased in female groups ($P<0.001$), however, both cFos and GFP expressions were increased significantly in male groups ($P<0.05$). No changes were seen in the dentate gyrus of the dorsal hippocampus (DG) in both genders (n=6). The effects of U50,488 were blocked by pre-administration of the KOPr antagonist norBNI (n=6 all treatment groups). The finding that in the CA1 region of the hippocampus cFos expression, but not cFos-driven GFP expression, was increased by U50,488 could reflect the temporal sequence, with downstream GFP expression occurring after cFos expression. Together these data suggest that KOPr activation induces cFos expression in the NAcc and prelimbic area of the PFC in male mice, both components of the 'reward' circuitry. These changes were not observed in female mice, supporting previous evidence suggesting sex differences in the behavioural effects of KOPr agonists. No sponsorship was received.

F21

IMIPRAMINE ATTENUATES THE BEHAVIOURAL EFFECTS INDUCED BY ABSTINENCE TO CHRONIC ETHANOL CONSUMPTION

Padovan CM, Psychology, University of São Paulo, Av. Bandeirantes, 3900, Cidade Universitária, 14040901, Ribeirão Preto, SP, Brazil, 14040901 cpadovan@usp.br

Tirapelli CR(1), Cardoso RC(2)

(1) Escola de Enfermagem de Ribeirão Preto, Universidade de São Paulo, Avenida Bandeirantes 3900, 14040-902, Ribeirão Preto, SP, Brazil.; (2) Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Avenida Bandeirantes 3900, 14040-900, Ribeirão Preto, SP, Brazil

Chronic consumption of ethanol (CCE) leads to the development of cardiovascular and psychiatric diseases, as well as neurodegenerative diseases, among others. Nevertheless, the abrupt interruption on ethanol consumption, known as abstinence, leads to symptoms of anxiety. Once abstinence is sustained, anxiety symptoms can evolve to depressive syndromes, which, in turn, can be responsible for relapse and back to consumption of ethanol. Data from the literature using animal models points to the involvement of serotoninergic system in the consequences of abstinence. Therefore, we sought to investigate whether Imipramine (IMI), a tricyclic antidepressant, would attenuates the effects induced by abstinence to CCE on anxiety and depression. Male adult wistar rats (7 weeks old) had free access to water (WATER) or an ethanol solution (EtOH; 6% v/v; semi-voluntary) during three weeks. Then, they were submitted to a 48 hours-period of abstinence. After that, they were tested in the Elevated Plus Maze (EPM). IMI (15mg/kg; Water/IMI n=24; EtOH/IMI n=23) or saline (SAL; 1ml/kg; Water/SAL n=24; EtOH/SAL n=22) was given 24, 19 and 1 hour before test. The number of enclosed arm entries (EAE) and percentage of entries (OAE) and time spent (TOA) in the open arms were registered. After behavioural test, animals returned to their home cage and remained undisturbed for three weeks, with free access to water and food. Then they were submitted to the Forced Swim test (FST), as described By Porsolt et. al (1977). A Two-way ANOVA was used to analyse data, being DRINK and DRUG the factors considered. Significance was set at $p<0.05$). IMI decreased EAE in WATER-treated rats (DRUG: $F1,80=12.5$; $p<0.05$). No effects of DRINK ($F1,80=0.05$; $p>0.05$) nor an interaction DRINKxDRUG ($F1,80=3.69$; $p>0.05$) were found on EAE. However, significant effects ($p<0.05$) of DRINK ($F1,80=9.04$), DRUG ($F1,80=14.38$), and an interaction DRINKxDRUG ($F1,80=6.23$) were observed on OAE. DRUG significantly affected TOA ($F1,80=16.3$; $p<0.05$), while DRINK did not ($F1,80=0.72$; $p>0.05$). However, a significant interaction DRUGxDRINK was found on TOA ($F1,80=14.8$; $p<0.05$). Together, these results show that EtOH abstinence induced a decrease on exploratory activity, which was attenuated by treatment with IMI. Similar results were found on the FST. Significant effects of DRINK ($F1,93=14.79$; $p<0.05$), DRUG ($F1,93=28.89$; $p<0.05$), and interaction DRINKxDRUG ($F1,93=5.18$; $p<0.05$) were described

for TTI, without changing LAT (DRINK: F1,93=0.06; DRUG: F1,93=0.13; DRINKxDRUG: F1,93=0.03; p>0.05). These results show that IMI decreased TTI in WATER and EtOH-treated animals. Our data suggest that the serotoninergic system plays a role on anxiety and depression induced by abstinence to CEC. Financial Support: CAPES and CNPq (471917/2014-1).

F22

REPEAT KETAMINE EXPOSURE INDUCES MICROSTRUCTURAL CHANGES IN MOUSE BRAIN TISSUE

Chesters RC, Basic and Clinical Neuroscience, IoPPN, Maurice Wohl Clinical Neuroscience Institute Kings College London 5 Cutcombe Road London, SE5 9RT robert.chesters@kcl.ac.uk

Wood TC(2), Vernon AC(1)

(1) As presenting author; (2) Department of Neuroimaging, Centre for Neuroimaging Sciences, De Crespigny Park, London SE5 8AF

Introduction: Ketamine is an increasingly popular drug of abuse amongst young adults, particularly in the UK. Chronic users experience deficits in cognition and spatial memory, alongside sub threshold psychotic symptoms [Morgan, C.J.A, Curran H.V., 2012. Ketamine use: A review. Addiction 107, 27-38]. The mechanisms driving these effects are unclear. Diffusion Tensor Imaging (DTI) studies in chronic ketamine users reveal changes in brain microstructure, particularly in white matter of the frontal lobe [Roberts, E.R. et al., 2014. Abnormalities in white matter microstructure associated with chronic ketamine use. Neuropsychopharmacology 39, 329–38]. However, these data are confounded by poor matching between subjects, particularly on measures of drug use, making it difficult to identify the specific effects of ketamine. In contrast, rodent DTI studies offer precise control of such variables and permit invasive post-mortem measurements to link neuroimaging to neuropathology. Methods: Male C57/Bl6 mice (aged 11-12 weeks) were exposed to ketamine (20 mg/kg, i.p.) (n=15) or saline (n=15) intermittently (once per day every 3 days for 30 days) or daily (once daily for 14 days). Ex vivo DTI magnetic resonance images were acquired and group-level differences in brain microstructure were analysed using a region of interest (ROI) based approach and general linear model statistics in IBM SPSS statistics 22. Multiple comparisons were corrected for using false discovery rate correction (FDR). The DTI metrics analysed were Fractional Anisotropy (FA), Medial Diffusivity (MD), Axial Diffusivity (AD) and Radial Diffusivity (RD). Results: In mice administered ketamine intermittently, ROI analysis revealed an increase in FA within the right corpus callosum (Cohen's D; 1.5) and a decrease in both FA and MD (Cohen's D; 1.26 & 0.89) in the cortex of the left frontal lobe ($p<0.05$, FDR corrected). In mice administered ketamine daily, DTI analysis revealed reduced MD, AD and RD in both the left and right corpus callosum (Cohen's D; 1.04, 1, 1.2 and 1.27, 1.17, 1.16 respectively) and the cortex of the left frontal lobe (Cohen's D; 1.41, 1.45, 1.36) ($p<0.05$, FDR corrected). Conclusion: These data provide preliminary evidence to suggest that there are similarities in the effects of ketamine on brain microanatomy in mice to that previously observed in chronic ketamine users. Specifically, decreases in both FA and AD have been observed in regions of the frontal lobe in both species. Studies are now underway to investigate the cellular correlates underlying the neuroimaging changes observed in mice. This study was funded by King's Health Partners.

F23

DISSOCIATION OF CONDITIONED PLACE PREFERENCE AND TOLERANCE TO SUCROSE IN PLANARIA

Mohammed Jawad RA, Neuroscience, Psychology and Behaviour, University of Leicester, University Road, Leicester, UK, LE1 7RH ramj1@leicester.ac.uk

Prados J(1), Hutchinson C(1)

(1) As presenting author

Introduction: Sucrose has been found to elicit addictive-like behaviours in rodents, like the development of tolerance and the association with cues present at the time of consumption (Avena et al., 2008, Neurosci Biobehav Rev, 32(1), 20-39). Furthermore, it shares the same neurochemical responses observed in the abuse of addictive substances like cocaine (Colantuoni et al., 2001, Neuroreport, 12(16), 3549-3552), (Avena et al., 2008, Neurosci Biobehav Rev, 32(1), 20-39). The experiment reported here addresses the effects of

sucrose on planarian behaviour. Planarian flatworms present a nervous system which resembles the nervous system of vertebrates both in structure (central and bilateral) (Denes et al., 2007, Cell, 129(2), 277-288) and physiology (with similar neurotransmitter systems including dopamine, serotonin…) (Søvik & Barron, 2013, Brain, behavior and evolution, 82(3), 153-165). Aim: The experiment aimed to determine whether planaria show addictive behaviour to sucrose; whether the development of addictive behaviour in planaria depends upon the same principles of learning that are known to rule these phenomena in vertebrates; and finally, whether Conditioned Place Preference (CPP) and Tolerance are controlled by the same neurochemical and behavioural mechanisms. Method: Thirty Two brown planaria (Dugesia) were used in this experiment. Animals in a control group were exposed to a 10% sucrose solution in one context, A, and plain water in a different context, B. However, animals in a second group were exposed to a 10% sucrose and a 1μM SCH 23390 (a dopamine antagonist) solusion in context A; and a 1μM SCH 23390 solution in context B. Results: Animals in a control group, developed CPP to the context A compared with animals in the second group. A One-Way ANOVA showed a significant differences between the groups, $F(1,30)=51.57, p<0.001$. However, the data of the tolerance test of the experiment showed that both groups developed tolerance to the effect of sucrose in context A. An ANOVA with Group (Sucrose vs. Suc& D-) and Context (Same vs. Different) showed a significant effect of Group, $F(1,30)=4.198, p<0.05, \eta p^2=.12$, and Context, $F(1,30)=11.96, p<0.01, \eta p^2=.28$; the interaction Treatment x Context was not significant $F<1$. Conclusion: The results show that the development of CPP and tolerance depend upon the same principles that rule learning in vertebrates; and allow for a dissociation of the CPP and tolerance phenomena. Source of financial sponsorship of the study is: University of Muthanna- IRAQ.

PD01

PREDICTING RESPONSE TO PSYCHOLOGICAL TREATMENT FOR DEPRESSION: COMBINING PSYCHOSOCIAL AND INFLAMMATORY MARKERS

Strawbridge R, Centre for Affective Disorders, Dept of Psychological Medicine, Institute of Psychiatry, Psychology & Neuroscience, King's College London, PO74 103 Denmark Hill, SE5 8AZ becci.strawbridge@kcl.ac.uk

Young AH(1), Cleare AJ(1)

(1) As presenting author

Introduction: A critical aspect of reducing the burden of depression is the need to increase the rate, and extent, of response to currently available treatments. No successful programs for doing so have yet been reliably implemented, although a wide range of psychological, clinical, demographic and biological factors have been linked with treatment non-response. While research in mood disorders suggests intricate links between depression and inflammatory states, this literature currently provides an inadequate description of the nature of the depressive disorders studied and involves extensive heterogeneity between patients and study methodologies. Methods: The study described examined a broad spectrum of circulating pro-inflammatory proteins before and after psychological interventions for depression, alongside a range of psychosocial, clinical and demographic variables. We tested specific hypotheses that raised inflammatory markers predict a poor response to treatment, to detect inflammatory changes during treatment in relation to clinical response. We anticipated that the prediction of treatment response would be stronger when considering non-inflammatory in conjunction with inflammatory predictors. Results:49% of participants responded to treatment. Pre-treatment depression severity and quality of life were poorer in participants with more severe depression after therapy. High levels of tumour necrosis factor (TNFα) and low interferon-γ (IFNγ) were also strongly predictive of post-treatment severity. Elevated pro-inflammatory markers interleukin-g (IL-6) and intracellular cell-adhesion molecule (ICAM1) also prospectively predicted non-response to therapy; while c-reactive protein (CRP) and chemokine CCL17 (TARC) were associated with a poor response cross-sectionally after therapy. A more prominently somatic than cognitive presentation of depression was found alongside higher inflammatory markers, but IL-6 and serum amyloid alpha (SAA) showed decreases alongside psychotherapy in these patients while most participants had higher levels of inflammatory proteins after treatment, regardless of symptom subgroup. Conclusions: This is, to our knowledge, the first study to have assessed a wide range of inflammatory proteins and psychosocial measures as potential predictors of response to psychological treatment for depression. Results suggest

that inflammation is associated with increased disability and provide novel evidence that these proteomic markers in combination with self-report information can predict response to psychological therapy. Further work may enhance the ability to predict treatment-response by assessing distinct, standardised treatment programmes and testing the replicability of these findings.

PD02

EARLY EFFECTS OF FLUOXETINE ON EMOTIONAL NEURAL PROCESSING IN DEPRESSED ADOLESCENTS

Capitao LP, Department of Psychiatry, University of Oxford, Neurosciences building, Department of Psychiatry, Warneford Hospital, Warneford Lane, Headington, OX3 7JX liliana.capitao@psych.ox.ac.uk

Harvey C-J(1), Chapman R(2), Murphy SE(2), James A(2), Cowen PJ(2), Harmer CJ(2)

(1) Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford OX3 9DU; (2) Univ Dept of Psychiatry, Warneford Hosp, Oxford OX3 7JX

Introduction: Fluoxetine is the first-line drug treatment for paediatric depression. Although the mechanisms of action of antidepressants are increasingly characterised in adults, there is little work on how they act in the developing brain. Here, we used functional neuroimaging to investigate the early effects of fluoxetine on emotional neural processing. This approach has proved useful in adults; indeed, previous research has shown that antidepressants act to reduce the negative bias that characterises depression early on in treatment and before clinical improvements become apparent [1]. Our aim was therefore to explore the acute effects of fluoxetine in depressed adolescents using functional neuroimaging. We predicted that a single dose of fluoxetine would reduce activation in the amygdala in response to anger, an emotion particularly relevant for adolescent depression. Methods: Forty-six adolescents were recruited: 29 patients with Major Depression and 17 healthy controls (13-18 years). After being prescribed antidepressant treatment by their psychiatrist, patients were randomised to receive their first fluoxetine dose (10mg) or placebo. 6-hour post administration, participants completed a gender discrimination fMRI task including angry, happy and fearful faces. Healthy controls did not receive any pharmacological intervention but completed the same neuroimaging task. Results: As predicted, participants on fluoxetine showed decreased activation in response to anger in our a-priori region of interest, the amygdala ($p<0.05$). Whole-brain analyses ($Z=2.3$, corrected spatial extent threshold of $p<0.05$) also revealed reduced activation in the occipital cortex in response to anger>happiness. These neural changes were seen in the absence of overall effects of fluoxetine vs. placebo on subjective symptoms, therefore representing a direct effect of the drug. When comparing depressed adolescents on placebo vs. healthy controls, differences in the prefrontal cortex emerged in response to anger>happiness, with healthy controls revealing higher activation in the orbitofrontal cortex. Conclusions: To the best of our knowledge, this is the first study that investigated the early mechanisms of fluoxetine in young people. These findings suggest that similarly to what is seen in adults, antidepressants act early to influence emotional processing in adolescents, an effect that is not mediated by subjective changes in mood. The effect on anger processing is consistent with our previous work showing that acute fluoxetine reduces accuracy to identify anger in young people aged 18 to 21 years old [2], and may therefore represent a key mechanism relevant to the treatment of paediatric depression, which is often characterised by co-existing symptoms of low mood and irritability. References: [1] Harmer CJ, Goodwin GM, & Cowen PJ (2009). Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. The British Journal of Psychiatry: The Journal of Mental Science 195, 102–108. [2] Capitao LP, Murphy SE, Browning M, Cowen P & Harmer C (2015). Acute fluoxetine modulates emotional processing in young adult volunteers. Psychological Medicine), 45, 2295–2308. Funding: This study was funded by grants from the John Fell fund and Medical Research Council (MRC). Liliana Capitao was funded by the Portuguese Foundation for Science and Technology (FCT) during her DPhil.

PD03

IMPROVING COGNITION IN PATIENTS WITH REMITTED DEPRESSION: IS MODAFINIL A FEASIBLE OPTION?

Kaser M, Psychiatry, University of Cambridge, University of Cambridge Department of Psychiatry, Herchel Smith Building for Brain and Mind Sciences Cambridge Biomedical Campus, Robinson Way, Cambridge, CB2 0SZ mk708@cam.ac.uk

Depression is the leading cause of disability worldwide. An important factor associated with poorer social and occupational functioning in depression is cognitive dysfunction (McIntyre et al. 2015, CNS Drugs, 29(7), 577-589.). Difficulties in concentration, memory are among the most common residual symptoms in depression (Conradi et al. 2011 Psychological Medicine, 41(6), 1165-1174.). Objective neuropsychological assessments document that cognitive deficits persist into remission and the magnitude of deficits are comparable to that of acutely depressed patients (Rock et al. 2014, Psychological Medicine, 44(10), 2029-2040). Cognitive deficits in depression also pose a risk for relapse (Fossati et al. 2003, Journal of Psychiatric Research, 38(2), 137-144.). Despite the significant impact on outcomes, cognitive dysfunction in depression is still underrecognized (McAllister-Williams et al. 2017, Journal of Affective Disorders, 207, 346-352). Most currently available treatments do not specifically address cognition in depression (Shilyansky et al. 2016, Lancet Psychiatry 3, 425–435.). Cognitive dysfunction in depression is an unmet clinical need, and alternative interventions are warranted (Kaser et al. 2017, Psychological Medicine, 47, 987-989.). Modafinil is a wake-promoting agent that showed beneficial effects on cognition in healthy volunteers as well as patients with neuropsychiatric conditions. Cognition-enhancing properties of modafinil could be a potential treatment option for cognitive dysfunction in depression. This talk will provide a general outline of cognitive dysfunction in depression and discuss the feasibility of modafinil for addressing persistent cognitive difficulties in depression. Findings from a recently published study using modafinil to improve cognitive functions in patients with remitted depression (Kaser et al. 2017, Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 2 (2), 115-122.) will be presented. The abovementioned study was funded by a core award to Behavioural and Clinical Neuroscience Institute from the MRC (Centre Grant G1000183) and the Wellcome Trust (Strategic Award 093875/Z/10/Z).

PD04

THE HIGHS AND LOWS OF PSYCHEDELICS IN THE TREATMENT OF DEPRESSION

Rucker JJ, Centre for Affective Disorders, The Institute of Psychiatry, Psychology & Neuroscience, 16 De Crespigny Pk, London, SE5 8AF james.rucker@kcl.ac.uk

Introduction: Recently there has been a resurgence of interest in the classical psychedelic drugs that include psilocybin (the active component of so-called ‘magic’ mushrooms) and d-lysergic acid diethylamide (LSD). Previously used by psychiatrists as pharmacological catalysts in psychotherapy before prohibition in the early 1970s, their therapeutic utility is now being re-investigated in a variety of non-psychotic mental health problems, including treatment resistant depressive disorder. Methods: In this open-label pilot study at Imperial College London, 20 patients with treatment-resistant, moderate-severe unipolar depressive disorder were withdrawn from their antidepressant medication under psychiatric supervision and treated with two doses of psilocybin (10 & 25mg) 1 week apart in a psychologically supportive clinical setting. Patients were followed up for 6 months. The primary outcome measure was the patient rated quick inventory of depressive symptoms (QIDS-SR). Results: Relative to baseline, reductions in depressive symptoms were observed for the first five weeks post treatment (mean QIDS reduction at week 1 = -10.2, 95% CI = -7.8 to -12.6, $p < 0.001$, Cohen’s d = 2.2; mean QIDS reduction at week 5 = -9.2, 95% CI = -6.7 to -11.7, $p < 0.001$, Cohen’s d = 2.3) with 12 and 9 patients meeting criteria for response and remission at week 3. Results remained positive at months 3 (mean QIDS reduction = -7.2, 95% CI = -4.2 to -10.2, Cohen’s d = 1.5, $p < 0.001$) and 6 (mean QIDS reduction = -6.5, 95% CI = -3.2 to -9.2, Cohen’s d = 1.4). Conclusions: Psilocybin with psychological support may be a promising new treatment for unipolar depressive disorder unresponsive to standard treatments. Further research is warranted to establish proof of efficacy in a randomised, controlled, blinded trial design. Trial sponsorship: UK Medical Research Council.

PW01

FOXO1, A2M AND TGFB1: THREE NOVEL GENES PREDICTING DEPRESSION IN GENE X ENVIRONMENT INTERACTIONS ARE IDENTIFIED USING CROSS-SPECIES AND CROSS-TISSUES TRANSCRIPTOMIC AND MIRNOMIC ANALYSES

Cattaneo A, Psychological Medicine,, Institute of Psychiatry, Psychology & Neuroscience, The Maurice Wohl Clinical Neuroscience Institute, Cutcombe Road, Brixton, London, SE5 9RT annamaria.cattaneo@kcl.ac.uk

Cattane N(1), Malpighi C(1), Czamara D(2), Binder E(3), Suarez A(4), Lahti J(4), Räikkönen K(4), Pariante CM(5), Dazzan P(6), Eriksson J(7), Kajantie E(7), Mondelli V (8), Luoni A(9), Riva MA(9)

(1) Biological Psychiatry Unit, IRCCS Fatebenefratelli S. Giovanni di Dio, Brescia; (2) Department of Translational Research in Psychiatry, Max-Planck Institute of Psychiatry, Munich, Germany; (3) Department of Translational Research in Psychiatry, Max-Planck Institute of Psychiatry, Munich, Germany;; (4) Institute of behavioral sciences, University of Helsinki, Helsinki, Finland; (5) Institute of Psychiatry, Psychology & Neuroscience; (6) Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK;; (7) National Institute for Health and Welfare, Helsinki, Finland; (8) Stress, Psychiatry and Immunology Laboratory, Department of Psychological Medicine, Institute of Psychiatry, King's College, London; (9) University of Milan, Department of Pharmacological and Biomolecular Sciences, Milan, Italy

INTRODUCTION: Depression results from the interplay of vulnerability genes with environmental factors, a phenomenon named as 'gene-environment (GxE) interaction'. To date, GxE interaction studies have been limited to hypothesis-based candidate genes, since genome-wide (GWAS)-based GxE interaction studies would require enormous datasets with genetics, environmental and clinical variables. METHODS: We performed transcriptomic and miRNomic analyses using RatGene 2.1st and miRNA 4.1st Arrays on a GeneAtlas platform (Affymetrix) in the hippocampus of adult rats exposed or not to prenatal stress (PNS); we then integrated these results with transcriptomic data performed with HuGene 2.1st Arrays in blood samples of 40 control subjects characterized for a history of childhood trauma. Statistical and bioinformatics analyses were performed with Partek Genomic Suite and Ingenuity Analyses Software for pathways and network analyses. Selected candidate genes were tested for GXE in two cohorts either with a range of childhood traumatic experiences (Grady Study Project) or with separation from parents in childhood (Helsinki Birth Cohort Study), where GWAS were available. We individually tested SNPs within the selected genes resulting from the final network analysis, calculating both nominal p-values and also multiple testing corrected p-values.

RESULTS: The transcriptomic and miRNOmic analyses identified a significant modulation of 916 genes and of 68 miRNAs in association with PNS ($1.2<FC<-1.2$, q-value<0.05); a mRNA-miRNAs combining analysis on the same animals allowed the identification of a panel of 528 top-hit genes that were both modulated by PNS exposure and targeted by the miRNAs that were modulated by PNS. These genes were involved in 42 pathways including Axonal Guidance, Protein Kinase-A Signaling, Glucocorticoid Receptor Signaling, TGF-beta Signaling, STAT3 Pathway, ILK Signaling and IL-8 signaling. We then overlapped these 528 genes with the 250 genes that resulted significantly modulated in the blood of subjects in association with childhood trauma, and we found 16 genes as modulated in the same direction. A network analyses on these 16 genes identified only one cluster of interacting genes, which was involved in inflammatory processes and glucocorticoid functionality. These genes were: Forkhead box protein O1 (FOXO1), Alpha-2-Macroglobulin (A2M) and Transforming Growth Factor Beta 1 (TGFB1).

FOXO1, A2M and TGFB1 were then tested for GxE interactions in the two clinical cohorts: six FOXO1 SNPs showed significant GxE interactions with emotional abuse in the Grady Study Project that survived stringent permutation analyses and were all replicated in the Helsinki Birth Cohort Study. In addition, other SNPs in all the three genes showed significant GxE interactions with emotional, physical and sexual abuse in the Grady Study.

CONCLUSION: We therefore provide a successful 'hypothesis-free' approach for the identification and prioritization of candidate genes for GxE interaction studies that can be investigated in GWAS datasets.

FUNDING:This work was supported by the grants "Immunopsychiatry: a consortium to test the opportunity for immunotherapeutics in psychiatry' (MR/L014815/1) and 'Persistent Fatigue Induced by Interferon-

alpha: A New Immunological Model for Chronic Fatigue Syndrome' (MR/J002739/1), from the Medical Research Council (UK). Additional support has been offered by the National Institute for Health Research Mental Health Biomedical Research Centre in Mental Health at South London and Maudsley NHS Foundation Trust and King's College London. Dr. Cattaneo is also funded by the Eranet Neuron 'Inflame-D' and by the Ministry of Health (MoH). Professor Raikkonen has received funding from the Finish Academy (No 7631758).

PW02

NEUROIMAGING IN PRECLINICAL MODELS AS A REFINED APPROACH TO PSYCHOPHARMACOLOGY RESEARCH

Vernon AC, Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King's College London, Maurice Wohl Clinical Neuroscience Institute 5 Cutcombe Road London United Kingdom, SE5 9RT anthony.vernon@kcl.ac.uk

The Vernon lab aims to address the lack of continuity between the levels of analysis used in animal models and clinical research in neuropsychopharmacology and psychiatric disorders. To fill this gap, we have developed a cutting edge, reverse-translational approach, comprising in vivo small animal neuroimaging, (clinically comparable technology), with post-mortem neuropathology and molecular analyses of gene and protein expression. We can therefore recapitulate precise correlates of specific neural systems in rodents to humans. We apply this systems level approach to address two research questions: First, we seek to understand the impact of chronic antipsychotic drug exposure on the nervous, immune and endocrine systems. Our work in this field has demonstrated that (a) chronic antipsychotic exposure decreases total rat neocortical volume; (b) an effect seen across different antipsychotics but distinct from other psychotropics such as lithium; (c) these effects are reversible on drug withdrawal; (d) these volume changes represent a loss of neuropil and (e) are putatively associated with microglial activation (Vernon et al., Biological Psychiatry, 2011; 69(10): 936-44; Vernon et al. Biological Psychiatry, 2012; 71(10): 855-63 and Vernon et al., Biological Psychiatry, 2014; 75(12):982-90; Cotel et al., Eur. Neuropsychopharmacology, 2015; 25(11): 2098-107). Second, we seek to understand how alterations in brain structure and function observed in patients with psychiatric disorders align with appropriate rodent models for these disorders. This is crucial to validate subsequent observations in animal models at the cellular and network levels. Our work in this field has primarily focussed on maternal immune activation (MIA), which is associated with increased risk for psychiatric disorders in the offspring. Utilising our translational approach, we have identified that exposure of rodent offspring to MIA in utero leads to aberrant brain maturational trajectories and abnormalities in myelin (Vernon et al., Eur. Neuropsychopharmacology 25(12): 2210-20; Vernon et al., Brain Behaviour and Immunity, 2017; 63:50-59; Richetto et al., Cerebral Cortex, 2017; 27(6): 3397-3413). Through collaboration we have also evaluated the validity of translocator protein (TSPO) as a disease-relevant marker of neuroinflammation (Notter et al., Molecular Psychiatry, 2017; doi: 10.1038/mp.2016.248). Our on-going work fuses these research questions to investigate how chronic exposure to antipsychotics affects TSPO and cortical thickness and how these relate to changes in brain microglia, synaptic pathology and ultimately, behaviour in the MIA model. Our goal is to advance our understanding of the impact of chronic antipsychotic treatment in a pathological context, to inform the clinical use of these drugs.

PW03

GLUTAMATE AND FUNCTIONAL MRS – A DYNAMIC DUO?

Stone JM, Psychology and Neuroscience, Inst of Psychiatry, King's College London, SE5 8AF james.m.stone@kcl.ac.uk

There has been considerable interest in the role of glutamatergic neurotransmission in schizophrenia over the last 3 decades, although definitive results are still elusive. Recently a number of groups using Magnetic Resonance Spectroscopy (MRS) have reported that medial prefrontal glutamate is elevated in patients with first episode psychosis who have failed to respond to antipsychotic drugs, leading to the hypothesis that poor responders might have a different underlying neurochemical abnormality. It has

been suggested that this finding might be used as a biomarker to stratify patients according to their likely response to antipsychotic drugs. On the other hand, elevations in brain glutamate and glutamine occur in response to acute challenges such as pain and ketamine administration, as well as changing dynamically with functional brain activity. MRS allows a snapshot estimation of brain glutamate and glutamine levels at a fixed point in time. However there has been some controversy as to whether the measured levels are derived from metabolic or neurotransmitter pools, and it is also not able to measure neurotransmitter response to stimuli. Functional Magnetic Resonance Spectroscopy (fMRS) allows the measurement of dynamic changes in brain glutamate and glutamine levels during brain activity, and may give a closer estimate of glutamatergic neurotransmission. In this presentation, I will review glutamatergic findings in schizophrenia. I will then present the results from some recent pilot work from my lab using fMRS in patients with schizophrenia and bipolar affective disorder. Lastly, I will consider whether functional MRS might be a useful technique in stratifying patients with schizophrenia according to treatment response.